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Comparison of phenanthridine with other aza-aromatic heterocycles

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COMPARISON OF PHENANTHRIDINE WITH
OTHER AZA-AROMATIC HETEROCYCLES

45
by

John Joseph Eisch

A Dissertation Submitted to the
Graduate Faculty in Partial Fulfillment of
The Requirements for the Degree of
DOCTOR OF PHILOSOPHY

Major Subject: Organic Chemistry

Approved:

Signature was redacted for privacy.

In Charge of Major Work

Signature was redacted for privacy.

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I. INTRODUCTION

Although phenanthridine, a nitrogen heterocycle isosteric with phenanthrene, is one of the constituents of coal tar (1), it was first obtained in 1884 by Graebe (2) when he passed benzalaniline through a red-hot tube. The characterization of this unknown base was subsequently accomplished by Pictet and Ankersmit (3) in 1889. Pictet and his group (4-10) studied this system during the next 15 years, but the field then lay dormant until 1930 when the discovery of a benzophenanthridine nucleus in certain alkaloids such as chelidonine and sanguinarine reawakened interest in phenanthridine (11). Shortly thereafter, Morgan and Walls began their fruitful researches on the fundamental chemistry of phenanthridine which in time led to the discovery of derivatives effective against trypanosomiasis in animals and children (12-20).

Despite the ample literature published on phenanthridine derivatives, our knowledge of the fundamental chemistry has progressed little from that established by the work of Morgan and Walls (12, 13) and Ritchie (21). In fact, the nitration of phenanthridine, first reported in 1932 (13), gave rise to mononitrophenanthridines which were not identified until 1952 (22). The complexity of the system, allowing nine

different mono-substituted derivatives, and the difficulty in synthesizing certain phenanthridine derivatives have deterred workers from developing its fundamental chemistry.

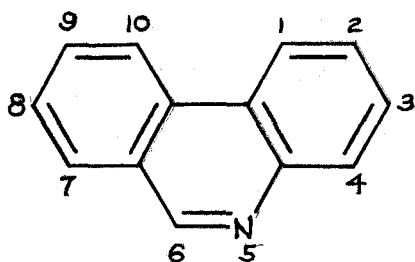
The purpose of this investigation is to elucidate the unresolved chemistry of phenanthridine and certain of its derivatives. The behavior of phenanthridine in electrophilic processes such as sulfonation, bromination and nitration is examined, as well as its susceptibility to the nucleophilic reactions of alkylation, hydroxylation and cyanation. Similar studies are applied to phenanthridone to develop the synthetic utility of this system. It also seems profitable to bring analogous reactions of other aza-aromatic compounds into sharp comparison with those of phenanthridine in order to highlight any differences in mode or ease of reaction.

As a framework and interpretative tool the modern theoretical views of molecular structure and reaction mechanisms are freely invoked in a discussion of the known chemistry of pyridine, quinoline, isoquinoline and acridine in relation to phenanthridine.

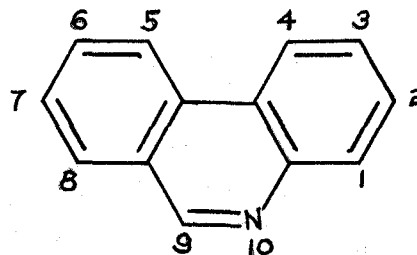
For an adequate survey of phenanthridine chemistry up to 1950, the reader is referred to the review of Theobald and Schofield (23). A more detailed and interpretative

discussion, but lacking a tabulation of compounds, is that of Walls (24).

The numbering system of phenanthridine advocated by Chemical Abstracts and The Ring Index (25) since 1937 is that shown in (I). The system employed previous to 1937 and still favored by foreign journals is given in (II). This system has the merit of paralleling that of phenanthrene. Nevertheless, for the sake of conforming to American usage, system (I) will be employed throughout this thesis.



I



II

II. HISTORICAL--COMPARISON OF PHENANTHRIDINE WITH OTHER AZA-AROMATIC HETEROCYCLES

A. Introduction

The fact that chemical knowledge gathered from the study of aliphatic compounds failed to account for the behavior of aromatic systems has been termed historically the "benzene problem". Eminent chemists from almost the beginning of organic chemistry have been intrigued by the unusual stability of these systems and the preference for substitution rather than addition reactions. It has been long recognized, moreover, that certain cyclic nitrogen compounds such as pyridine also possessed this aromatic character. Thus an analogous "pyridine problem" arose. Here, indeed, the experimental facts were even more puzzling. Not only did pyridine derivatives have unique properties such as basicity, but they underwent reactions with sodium amide and potassium hydroxide (26, 27) with a facility unknown to benzene.

The wide diversity and reactivity of cyclic nitrogen derivatives have created a voluminous literature containing many monographs which consider in detail the known chemistry of individual heterocycles (28, 29). At the same time

theoretical chemists have advanced numerous explanations for the chemical and physical properties of these nitrogen compounds. Since the "pyridine problem" was an offspring of the "benzene problem", it is fitting that the pyridine solution should also be derived from the satisfactory resolution of the "benzene problem".

It is the purpose of this review to compare the analogous chemistry of these aza-aromatic heterocycles and their characteristic derivatives in terms of our present experimental and theoretical knowledge. The utility of modern views of molecular structure and reaction mechanisms will be examined, and their limitations pointed out.

The discussion will center around those six-membered nitrogen heterocycles having a formal set of conjugated double bonds. Furthermore, considerations will be largely limited to the monoaza-aromatic heterocycles, pyridine, quinoline, isoquinoline, acridine and phenanthridine. The behavior to be expected of polyaza-aromatic heterocycles such as quinoxaline and triazine usually involves a reasonable extrapolation of the chemistry of the monoaza-aromatic systems. Five- and seven-membered heterocycles such as pyrrole and azepine will not be considered.

Phenanthridine, a nitrogen isoster of phenanthrene, is taken as the focal point of these considerations. There are

several valid reasons for this. First, of the five basic heterocycles mentioned previously, it is the one whose individual chemistry has been least elucidated. Recently, however, the nitration (22) and bromination (30) of this system have been successfully carried out. Hence, by consideration of the known behavior of other heterocycles, the gaps in the knowledge of phenanthridine chemistry will be apparent. Second, since its molecular asymmetry presents nine non-equivalent positions for substitution, phenanthridine may subject any theory of substitution to a more rigid test. Factors determining the preferred site of substitution can be more carefully evaluated with such a complex system. Third, the discovery of the trypanocidal potency of certain phenanthridine derivatives (14) and their general bacteriostatic properties (31) has given the phenanthridine system a new-found physiological significance.

B. Aromaticity

Pre-electronic interpretations of the aromatic character of pyridine closely paralleled the explanations proposed for the behavior of benzene. Korner and Dewar (32) proposed a cyclic structure of alternate oscillating double bonds analogous to Kekule's representation of benzene (33), and

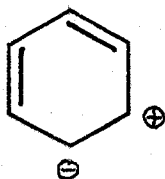
shortly afterwards Reidel (34) supported a Dewar structure containing a para bond between the nitrogen and gamma carbon. This was followed by a centric structure advanced by Bamberger (35). Perhaps the representation of pyridine most in accord with modern views was that based on Thiele's theory of partial valences (36). It would be over-demanding to expect that a fully satisfying solution to the problem of aromaticity would predate our knowledge of molecular structure and the nature of chemical bonding. Thus, the subsequent discovery of the electronic theory of valence (37, 38) coupled with newer experimental techniques gave a firm foundation to the more satisfying views which were to follow.

The discovery of the electron and the postulation of its role in chemical bonding laid the stage for a more intimate understanding of chemical behavior. The statement by de Broglie (39) that small particles such as electrons should exhibit wave properties was experimentally confirmed by Davisson and Germer (40) who showed that an electron beam could indeed be diffracted. Schrödinger (41) and Heisenberg (42) independently began to give mathematical expression to these wave properties of matter. Heisenberg's uncertainty principle postulated that both the energy and position of an electron could not be exactly determined. The position

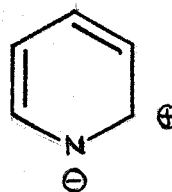
of an electron in an atomic field was therefore expressed as a probability function, which resulted in electron density patterns. Application of quantum mechanical calculations to such simple systems as the hydrogen molecule gave excellent results (43), but extension to larger molecules in a similar manner was unfeasible due to mathematical complexities. Consequently, the search was undertaken to develop simplified, approximate methods which would still yield useful information. In the study of aromatic systems factors to be unified and rationalized include: inherent stability of such systems; orientation of substituting species; and relative reactivities of related aromatic compounds. Considerable success has been realized in accomplishing these goals, but certain facets of present theory are quite unsatisfactory. Oftentimes the divergence from theoretical predictions indicates the importance of certain factors neglected in the simplified treatment.

Two approximate methods of treating aromatic compounds such as benzene and pyridine are the valence bond method and the molecular orbital method. Both methods have commendable features, but they are different approaches to the same problem. Neither is intrinsically a more accurate description of the molecule, but in certain instances one method may prove more convenient than the other.

For the organic chemist the valence bond method has the advantage of beginning with the classical, pre-electronic valence formulae and treating them according to wave mechanical principles. In the approach of Hückel (44), Pauling and Wheland (45) a fair approximation of the molecular wave function for benzene was found to be a linear combination of the two Kekule and the three Dewar structures. This set of valence bond formulae is a complete but not a unique set, as others could be used. Solution of the wave equation tends to be more complicated since one employs many-electron functions and takes account of electron spin. The result will be a unique structure of lowered energy, difficult to express in common structural symbols, but whose nature can be judged from coefficients of the contributing structures. There are other ionic structures which do not contribute significantly to the ground state of benzene (III), but are important in pyridine (IV).



III



IV

Invoking such ionic structures is useful in explaining chemical reactivity of nitrogen heterocycles. Daudel (46) has carried out a valence bond treatment of pyridine.

The molecular orbital approximation assumes that the atoms composing the molecule of benzene are arranged as they are in the final molecule. The electrons constituting the skeletal framework of the molecule (sigma electrons) are then fed in. Due to the geometry of these bonds, little interaction other than covalent bond formation will take place. However, since the carbon atoms have formed a planar hexagon by assuming sp^2 hybridization, each carbon atom has a p orbital extending above and below the plane of the ring. Since these p orbitals overlap, they interact to form three pi orbitals of lower energy and three of higher. Hence, the six remaining electrons upon being fed in will occupy the three lowest lying molecular pi orbitals. The diminution of energy upon the overlapping of the p orbitals is explained by the delocalization of the p electron to a pi orbital spread out above and below the ring (47). As in the wave particle in a box the energy is diminished by increasing the positional latitude of the particle. The results of molecular orbital calculations on such systems are considerably simpler, but they do not lead to any structural formulae. Instead a molecular diagram giving data on charge density,

bond order and free valence is indicated. The avoidance of classical molecular formulae is a merit of the method as it obviates the often misunderstood notion of resonance hybrids. Nevertheless, the enlightened use of valence bond structures is quite advantageous in certain qualitative considerations. Semi-quantitative calculations, on the other hand, are more readily made by means of the molecular orbital method. A close consideration of the treatment of the pyridine molecule by the method of molecular orbitals will be given later. The utility, scope and limitations of such calculations are not often stressed. Consequently, it is important that organic chemists be aware of the approximations involved and the accuracy of such calculations.

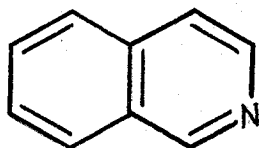
C. Theoretical Views of the Chemistry of Aza-aromatic Systems

1. General considerations

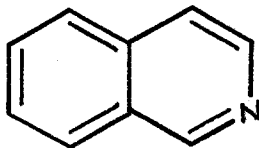
An adequate theoretical treatment of aza-aromatic heterocycles must rationalize not only the stability of the ring system but the different orientations of substitution encountered when cationic, anionic and free radical reagents are employed. Moreover, the basicity and dipole moments of these systems must be accounted for.

2. Bond fixation

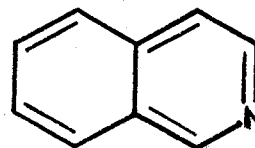
As a consequence of the electronic theory of valence it was realized that the basicity of these nitrogen compounds could be owed to the unshared electron pair on the nitrogen and that the dipole moment was a manifestation of the electronegativity difference between carbon and nitrogen. Prior to quantum mechanical treatment of these systems, previous attempts to rationalize reactivity have been based on the concept of "static bonds" in these heterocycles. For example, such proposed formulae for isoquinoline were



V



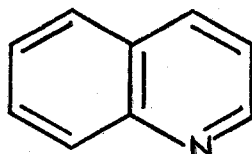
VI



VII

and by chemical reactivity (V) was adjudged a better representation of isoquinoline than (VII), since certain anionic reagents added to the system in a 1,2 rather than a 2,3 manner. (VI) was considered less satisfactory than (V), because according to the Fries rule, (VI) had only one fully aromatic ring. This idea of "static bonds" has persisted up to the present time with certain authors. Renshaw,

Friedman and Gajewski (48) coupled the known aminoquinolines with diazonium compounds. Assuming that coupling will occur ortho to the amino group only if a double bond intervenes, or para if two double bonds are present, these workers found that the sites of reaction were in accord with Erlenmeyer's structure of quinoline (VIII).



VIII

However, the fact that quinoline does indeed have a resonance energy (69 kilocalories per mole) means that other resonance structures make appreciable contributions to the resonance hybrid. Even if the Erlenmeyer structure were to be the largest single contributor to the linear combination function, the delocalization or resonance energy would make the resulting unique structure of still lower energy. Similar objections to other "static bond" structures cast doubt on the validity of the viewpoint.

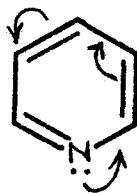
Another approach to the rationalization of the chemical behavior of nitrogen heterocycles has been forwarded by

Bergstrom (49). Extending Franklin's ammonia system of compounds, Bergstrom considered the C=N linkage as an ammono aldehyde and hence viewed quinoline as a cyclic ammono aldehyde ether in this system of compounds. All the addition reactions to the azomethine linkage could be correlated with the behavior of aldehydes in similar cases. Derivatives substituted in the alpha position such as amino, halo, hydroxyl and methyl could be compared with amides, acid halides, acids and methyl ketones. Explanation of similar behavior of the gamma, but not the beta, position rested upon Fuson's principle of vinylogy (50) by which the gamma position was a vinylogous alpha position. This implicitly assumes bond fixation to that represented by Erlenmeyer's formula (VIII).

These views give a fair understanding of chemical behavior but they do not take cognizance of modern advances in molecular structure. Besides, the use of chemical reactivity to determine electronic configurations is somewhat unsatisfactory, since the molecule will be perturbed by different reagents to varying degrees.

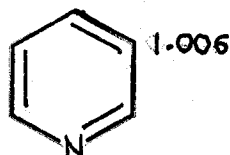
3. Quantum mechanical treatment of aza-aromatic heterocycles

The modern concepts of aromaticity as evolved from quantum mechanical considerations is easily extrapolated to heterocycles such as pyridine, quinoline and phenanthridine. Due to the presence of the nitrogen, certain changes must be made in the treatment. The most apparent property distinguishing these compounds from carbocycles is basicity. This stems from the unshared pair of sp^2 hybridized electrons on the nitrogen. Since this orbital extends out from the nitrogen in the plane of the ring, it cannot overlap with the π -electron cloud which has a node in the plane of the ring. This is theoretically significant because some workers (51) have suggested electromeric interactions whereby this electron pair would enhance the electron density at the beta position (IX).

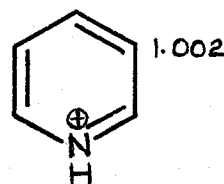


IX

However, the non-overlapping or orthogonality of the sigma and pi orbitals rules out such interactions. Another consequence of this orthogonality is that fixation of a proton on the nitrogen will disturb the pi cloud only by increasing the effective electronegativity of the nitrogen atom. This point is made because the reduced reactivity of pyridine is often explained (52) in terms of this positive pole present in acid solution, analogous to the anilinium ion. Such a view neglects the difference in electronic shifts in forming these two cations. This is reflected in the difference in the behavior of aniline and its ion. On the other hand, pyridine gives the same orientation as its ion. The anilinium ion has a reduced reactivity because fixation of a proton on the nitrogen changes hybridization from sp^2 to sp^3 . Calculations (53) indicate the pyridinium ion (XI) will have only a second-order diminution of charge density at the beta position compared with the unprotonated molecule (X).



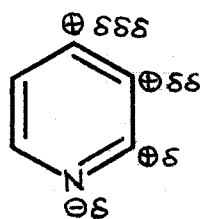
X



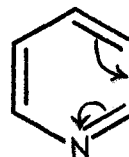
XI

A valence bond view of pyridine should take account of two electronic effects caused by substituting the CH in

benzene by N. First, the inductive effect of the electro-negative nitrogen withdraws electrons toward the nitrogen by the sigma bond framework in the order, alpha > beta > gamma carbon (XII). Second, due to the pi cloud the alpha and gamma carbons will be further depleted of pi electrons (XIII).



XII



XIII

It is clear that such heterocycles will have unequal charge distributions. The physical consequence will be the generation of a dipole moment, whereas chemically the pyridine molecule should be quite susceptible to anionic attack at the alpha and gamma positions.

The molecular orbital treatment of aza-aromatic heterocycles has been considered by many workers including Coulson and Longuet-Higgins (54), Dewar (55), Wheland and Pauling (56) and the French school of Pullman (57). Although the method involves fairly simple calculations and gives interesting results, some rather formidable assumptions make the results subject to certain reservations.

As a trial wave function for energy calculations the assumption is made that an approximate wave function (Ψ) is that obtained by taking a linear combination of the nitrogen p orbital wave function and the five carbon 2 p orbital wave functions:

$$\Psi = C_1\Psi_1 + C_2\Psi_2 + C_3\Psi_3 + C_4\Psi_4 + C_5\Psi_5 + C_6\Psi_6$$

This is substituted in the Schrödinger wave equation.

$$E = \frac{\int \Psi H \Psi d\tau}{\int \Psi^2 d\tau}$$

$$E = \frac{\int (\sum_{n=1}^6 C_N \Psi_N) H (\sum_{n=1}^6 C_N \Psi_N) d\tau}{\int (\sum_{n=1}^6 C_N \Psi_N)^2 d\tau}$$

where E = energy of the system,

H = Hamiltonian of the system,

$d\tau$ = spatial increment.

This expression is expanded and the integrals obtained are denoted thus.

$$\int \Psi_N H \Psi_M d\tau = \int \Psi_M H \Psi_N d\tau = H_{MN} = H_{NM}$$

$$\int \Psi_N \Psi_M d\tau = \int \Psi_M \Psi_N d\tau = S_{MN} = S_{NM}$$

The energy equation is then partially differentiated according to each coefficient to give six differential equations,

$$\frac{\partial E}{\partial c_n}, n = 1, 2 \dots 6.$$

By the variation theorem (58) a minimization of energy can be obtained by setting each resulting equation equal to zero. The first of the resulting secular equations is

$$c_1(H_{11} - ES_{11}) + c_2(H_{12} - ES_{12}) + \dots + c_6(H_{16} - ES_{16}) = 0$$

Now, in order to simplify solution of these equations the following assumptions are imposed:

$$H_{NN} (n = 3, 4, 5) = q = \text{Energy of a carbon } 2p \text{ electron localized on a carbon atom (coulomb integral of carbon).}$$

$$H_{NN} (n = 1) = q + x\beta = \text{Energy of electronegative nitrogen atom for its } 2p \text{ electron.}$$

$$H_{NN} (n = 2, 6) = q + \gamma\beta = \text{Energy of } \underline{\text{alpha}} \text{ carbon } 2p \text{ electron made more electronegative by adjacent nitrogen.}$$

$$H_{N,N+1} = \beta = \text{Resonance integral (non-adjacent} = 0)$$

$$S_{NN} = 1 \quad (\text{For normalized wave function})$$

$$S_{NM}(N \neq M) = 0 \quad (\text{Neglect of overlap})$$

Rewriting the equations and using these approximations, one obtains this determinant:

$$\begin{vmatrix} (q-E+x\beta) & \beta & 0 & 0 & 0 & \beta \\ \beta & (q-E+y\beta) & \beta & 0 & 0 & 0 \\ 0 & \beta & q-E & \beta & 0 & 0 \\ 0 & 0 & \beta & q-E & \beta & 0 \\ 0 & 0 & 0 & \beta & q-E & \beta \\ \beta & 0 & 0 & 0 & \beta & (q-E+y\beta) \end{vmatrix} = 0$$

Useful results can be obtained by solving this determinant for the six roots of E expressed in terms of q and β . However, the two parameters x and y must be assigned values to account for the decreased energy of a coulomb integral of an electronegative atom (β has negative sign). Unfortunately, no perfectly reliable method is known to estimate these

values. Therefore, the error introduced by this uncertainty outweighs the other assumptions of the method. Depending upon the values chosen the calculated pi electron densities of pyridine vary a great deal. This is illustrated by the data given in Table 1. The most promising approach to estimating x and y seems to be the calculation of the dipole moment of pyridine by the vector addition of the pi and sigma dipole contributions. With $x = 0.6$ Löwdin (62) obtained a calculated moment of 2.36 D for pyridine, whereas

Table 1. pi Electron densities of pyridine and values chosen for parameters x and y

Calculated <u>pi</u> electron densities in pyridine				x	y	Ref.
N	C _{α}	C _{β}	C _{γ}			
1.59	0.85	0.95	0.82	2.0	0.25	54
1.59	0.83	0.96	0.82	2.0	0.2	56
1.274	0.946	0.980	0.874	1.0	0.4	59
1.327	0.901	0.982	0.910	0.9	0.1	61
1.264	0.920	0.983	0.934	0.6	0.0	60
1.234	0.909	1.006	0.940	0.6	0.0	53
1.190	0.932	0.993	0.958	0.48	0.0	53

Orgel and co-workers (63) obtained a value of 2.15 D when x was taken as 1.0. In correlating Hammett sigma values with pi electron densities of heterocycles, Jaffe (64) adjusted the value of x to give the best fit of values and found $x = 0.59$ to give good agreement. However, the experimental value of 2.15 D for pyridine's dipole moment was recently obtained by microwave spectroscopy (65) and this tends to support a value of $x = 1.0$.

The charge densities could be calculated by substituting the different values of E in the above determinant and obtaining the coefficients of the molecular wave functions. Calculations are simplified, however, by using first order perturbation theory (54). This is especially advantageous with molecules such as phenanthridine where the molecule is treated as a perturbed phenanthrene (54). As the parent carbocycle has more symmetry, the calculations can be simplified by group theory (66). The error introduced by use of perturbation methods is well within the uncertainty caused by the estimation of x .

Besides the charge densities of the different atoms in aza-aromatic heterocycles, free valence and mobile bond indices can also be calculated. Free valence indicates the bonding tendency of an atom and it is roughly linearly related to the polarizability of the atom. Mobile bond

order measures the multiple bond character of a chemical linkage (47).

The chemical interpretation of these results is summarized thus (54). The assumption is made that all chemical reagents attack the heterocyclic substrate in one of three manners: first, by electrophilic or cationic attack such as nitration; second, by nucleophilic or anionic attack such as amination with potassium amide; or third, by free radical processes such as phenylation with benzoyl peroxide. Electrophilic reagents will attack the heterocycles at sites of high charge density and nucleophilic reagents will seek out positions of low electron density. It is believed that free radical reagents prefer positions having a high free valence index. Moreover, some interesting conclusions were reached in a study of the charge densities of a series of nitrogen heterocycles. First, the effect of aza substitution on pi electron density diminishes with the distance between the site of substitution and a given atom. Second, the effect of replacing an additional CH by N should be additive. Third, the greater the net charge at a position (either + or -), the more reactive it is to a charged reagent (- or +). Fourth, when there is little difference in the charge densities of positions, the polarizabilities of the positions become important.

Although this view of chemical reactivity is valuable, it is clear that serious objections can be raised to the statement that there is an "undoubted correlation between calculated electron distribution and the observed chemical behavior" (54). The nitration, bromination and sulfonation of quinoline point up several weaknesses in this unified approach. For electrophilic attack the calculated charge densities favor $C_8 > C_6 > C_3$. Sulfonation does indeed occur at C_8 , but a temperature factor is involved, as C_6 is attacked at higher temperatures (67). Bromination occurs at C_3 , although C_8 and C_6 seem more preferable from theory. If there is little difference in reactivity among the three positions, one would expect that the 8- and 6- isomers would also be found, but this is contrary to experiment (68). Finally, nitration occurs mainly at C_5 with less at C_8 (69). This indicates that charge density predictions are of little help in this case. These difficulties in utilizing the charge densities of heterocycles to predict sites of substitution have been attributed to the importance of neglected factors. From this stemmed the realization that changes in electronic configuration required to attain the transition state of the reaction might often be a predominant factor in determining the site of reaction (70). Another aspect, seriously ignored in the charge density approach, is the

specific nature of the reagent. The behavior of quinoline with the three different electrophilic reagents mentioned above illustrates the importance due the reagent. Until Brown's work (71, 72), which will be discussed shortly, there was little concern over whether different electrophilic species might vary in their electronic demands upon the aromatic system in the course of reaction. Thus, a complete theoretical treatment of these aza-aromatic heterocycles necessitates consideration of many other factors besides the groundstate charge distribution of the substrate heterocycle. The following discussion will highlight those factors which must be weighed in the synthesis of a satisfactory rationalization of aza-aromatic chemical behavior.

4. Transition state treatment of aromatic substitution

In the transition state view of chemical reactivity one reflects upon the electronic alterations undergone in the course of reaction. The variation in the energy of a system is considered as the substituting reagent interacts with the aromatic substrate to form a new bond as the old bond of the displaced group is stretched until the group is expelled. It is felt that a high energy intermediate may be formed as (XV) with the two transition states (XIV and XVI) involved

in getting in and out of such a state. The transition state of higher energy will determine the rate of substitution as the reaction proceeds along the reaction coordinate x (Figure 1).

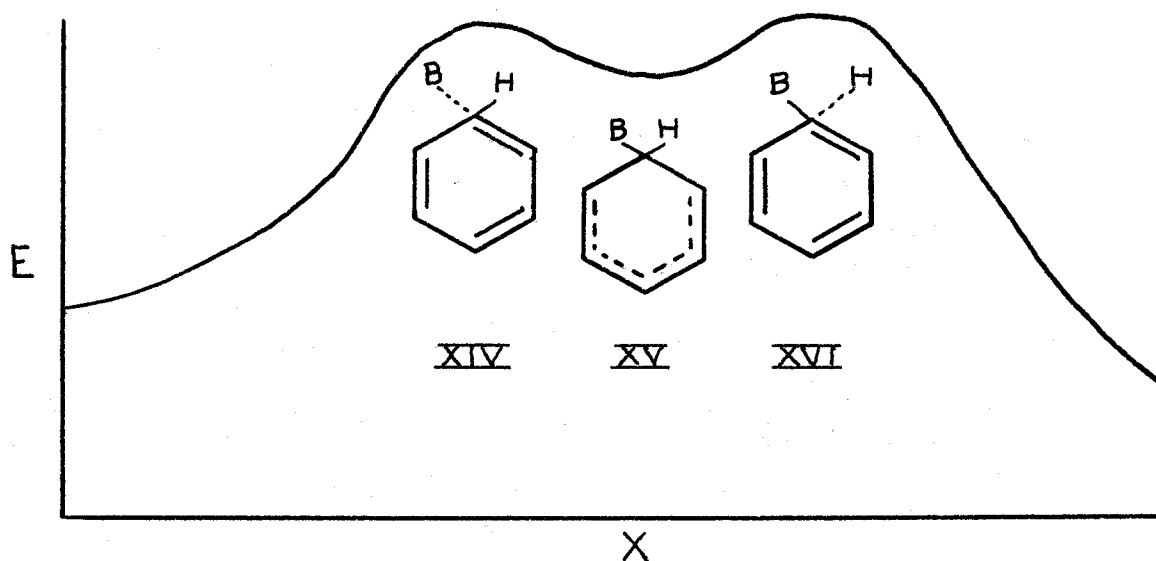


Figure 1. Variation of the potential energy along the reaction coordinate x

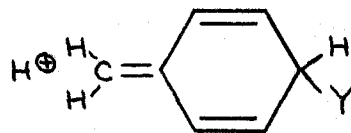
The energy of activation (E^\ddagger) is the difference between the energy of the rate-determining transition state (XIV or XVI) and that of the ground state of the reagents. If different aromatic carbon atoms are present in a molecule, substitution should occur preferentially at that carbon atom having the lowest E^\ddagger . One could then make an accurate prediction of preference in aromatic substitution if there were some manner to assess the energy of the transition state. Due

to the uncertainty in the exact configuration of this transition state, any semi-quantitative calculations must be based upon an assumed model for this state.

In substitution reactions occurring at aromatic carbon atoms it is likely that the original sp^2 hybridization is transformed to approximately an sp^3 or tetrahedral configuration (See XV in Figure 1) in the course of reaction. Consequently, Wheland (70) sought to assess the loss of resonance energy of various aromatic systems by taking such a tetrahedral configuration for the transition state model. The resonance energy of the tetrahedral model was calculated by the method of molecular orbitals. The resonance energy of the transition state, minus the resonance energy of the ground state obtained in a similar fashion, gave the loss in stabilization (W_B) in going to the transition state. The quantity W_B was taken as an index of E^\ddagger . Hence, the fact that naphthalene is attacked usually at the 1- position rather than at the 2- position, is rationalized by the fact that $W_{B1} < W_{B2}$. The method can be applied to electrophilic, nucleophilic, and free radical attack. Applied to pyridine, the method gave results in general accord with experiment.

Since the chemical reactivity of aza-aromatic systems can be interpreted either in terms of the ground state electronic distribution of the heterocycle, or the loss of

resonance energy in attaining a tetrahedral transition state, the choice between the two approaches will depend upon the position of the transition state along the reaction coordinate x in Figure 1. Both views, however, express extremes of the actual case. As the electrophilic reagent is varied from nitric acid through bromine to sulfuric acid, one might expect a variation in the electronic perturbation of the substrate aromatic compound and hence, a shift in the nature of the transition state. Recent studies by Brown and co-workers (71, 72) give experimental foundation for this view and showed that the nature of the reagent is important. These workers computed the relative rates of electrophilic substitution of benzene and toluene. With a given reagent a high $r(\text{toluene})/r(\text{benzene})$ was taken as evidence that the transition state in toluene received considerable hyperconjugative aid and hence the transition state resembled a tetrahedral configuration at the carbon atom attacked (XVII).



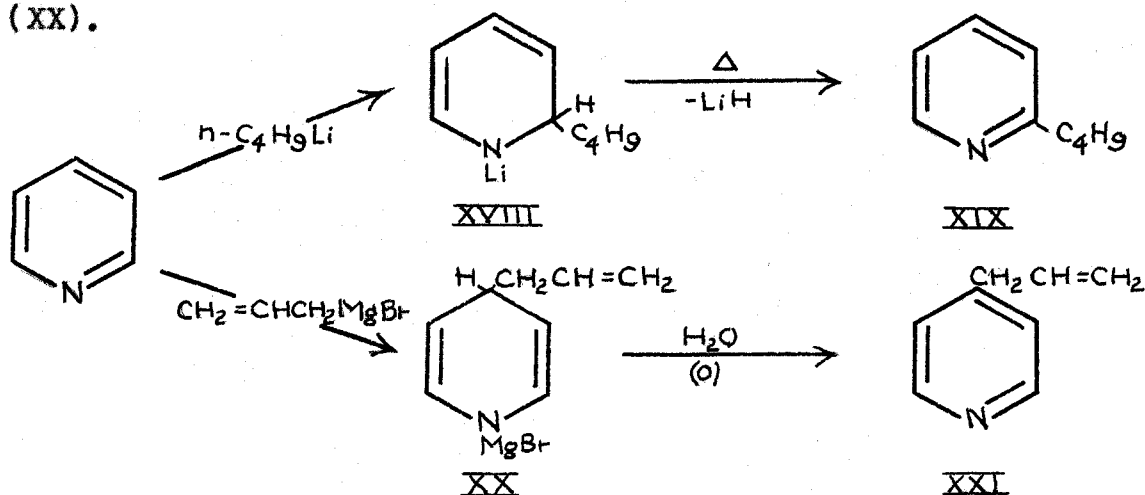
XVII

Conversely, a low ratio suggested the transition state had been reached before a tetrahedral configuration had been attained.

As it did not receive hyperconjugative aid, such a reagent was considered more reactive. In a parallel study the meta-para ratios for the attack of the same reagents on toluene were determined. A high value of meta/para suggested that the reagent under consideration had a lower selectivity than one yielding a low meta/para value. In such a manner it was observed that reagents having a high reactivity had a low selectivity (nitric acid), whereas those reagents exhibiting a lower reactivity had a higher selectivity (bromine). (Two exceptions, sulfonation and mercuration, are explicable in terms of proton elimination being the rate-determining step.) Electronically, this correlation may be interpreted thus. Since the more reactive reagents attain a transition state which is shifted from the tetrahedral model toward the reactants, the site of attack on the aromatic system will depend less on the localization energies and more on the charge densities and autopolarizabilities of the aromatic ground state. Thus, more reactive electrophilic reagents have sufficiently strong cationic centers to polarize the aromatic π cloud at longer distances and to cause interaction. These looser transition states may consist of a longer new bond or a non-localized π complex.

As will be discussed later, aza-aromatic heterocycles tend to undergo reaction with organometallic reagents in

which the net effect is substitution. However, the intermediate is stable enough to be isolable (73). Organolithium reagents attack the alpha position of pyridine (XVIII), whereas allylmagnesium bromide attacks the gamma position (74) (XX).



An explanation of this difference in behavior may lie in the following facts: n-butyllithium is an extremely vigorous nucleophilic reagent, attacking the heterocycles from pyridine to phenanthridine readily even at low temperatures. Allylmagnesium bromide, on the other hand, is a selective nucleophile toward aza-aromatic heterocycles, since it yields only 9% of product with pyridine and gives 81% with acridine. If Brown's correlation on electrophilic attack is extended to nucleophilic attack, one sees that the extremely reactive n-butyllithium will attain a transition state shifted toward the ground state where charge density and autopolarizability favor attack at the 2-position (75).

With the less reactive allyl Grignard reagent the transition state should be close to tetrahedral. Invoking Hammond's thermic postulate (76), one can then say that since the latter transition state resembles the 4-allyl-1,4-dihydro magnesium bromide product geometrically, it must also resemble the product in energy. Consequently, this product or the dihydro derivative obtained upon hydrolysis is a fair model for the transition state. Hence, the respective localization energies for the alpha and gamma positions will become important. Since 1,4-dihydropyridines (XXI) seem to be more stable than 1,2 dihydro derivatives (77) (XIX), the activation (localization) energy may be lower for an attack on the gamma position in pyridine by selective nucleophiles. Other examples of the preference of selective nucleophiles to attack the gamma position will be mentioned later.

D. Factors Affecting the Mode of Attack on Aza-aromatic Systems

1. Species undergoing attack

The approximate calculations leading to ρ electron densities and indices of free valence have already been discussed. It was further stated that the pyridinium ion,

present in electrophilic processes, differed in degree and in kind from the "positive pole" anilinium ion. It is conceded, however, that the charged nature of the pyridinium ion should somewhat hinder electrophilic attack by both the direct field effect and the decrease in the polarizability of the pi cloud. On the contrary, such complexes as the 1-methylpyridinium ion or 1-oxide greatly enhance the reactivity of the alpha and gamma positions toward nucleophilic attack. Here there is increased electronegativity of the hetero atom, further diminishing the electron densities of these positions. No information is available on the effect of protonation on the facility of attack by free radicals. If the polarizability of the site attacked is a dominating factor, the lessened polarizability of the protonated heterocycle should decrease its reactivity.

As detailed discussion will later show, there is often an increase in reactivity to a given reagent as one passes through the series, pyridine, quinoline, isoquinoline, phenanthridine and acridine. This holds true for electrophilic, nucleophilic and free radical attack. In the light of previous comments on the relation between the reactivity of reagents and the nature of the transition state, no one explanation is complete. The possible contributing factors can be summarized. First, the alpha and gamma carbon atoms

become more positive as this series is ascended, but the remaining carbon atoms tend toward greater polarizability.

This is especially true of dibenzopyridines where the perturbing nitrogen is more distant. Hence, reactivity toward both nucleophilic and electrophilic reagents increases.

Second, the localization energy required to remove a p orbital from conjugation with the pi cloud becomes progressively less in this series of heterocycles.

A point should be made concerning the term of "substrate" for the heterocycle. This is arbitrarily applied for convenience. Previously it was said that with a given substrate, a more reactive reagent shifted the transition state toward the ground state. Conversely it is also true that with a given reagent a more reactive heterocycle will also shift the transition state to the left.

2. Attacking species

Brown's (71, 72) work has shown that indeed the nature of the electrophilic species does determine the electronic demands to be made by the reagent. The correlation is applicable to electrophilic attack on aza-aromatic heterocycles and can be extended to cover nucleophilic attack as well. It would be interesting to determine how the behavior

of the fairly stable triphenylmethyl radical compared with the reactive phenyl radical in the reaction with pyridine.

It is well to remember that experimental conditions can alter the nature of a species. For example, electrophilic chlorination may occur through a number of species, Cl_2 , $\text{HO}_2\text{Cl}^\oplus$, HOCl or Cl^\oplus , depending upon conditions. Also the species could be changed from electrophilic to free radical in character.

3. Reversibility

The reversible nature of some substitution reactions is important in that such reactions tend to obscure the first choice of an attacking species. As a reversal of a substitution reaction will pass through the same reaction configurations as did the forward process (microscopic reversibility), the activation energy of the reverse process will be the activation energy of the forward reaction plus its thermodynamic heat of reaction, $E_{\text{rev}}^\ddagger = E_{\text{forward}}^\ddagger + \Delta H$. Reversibility of highly exothermic processes such as nitration is extremely rare. One reported case cites the formation of 4-nitroacenaphthene from 2-nitroacenaphthene (78). Much more common are reversible sulfonations and brominations (67).

Similar to the classical sulfonation of naphthalene, quinoline yields under moderate conditions quinoline-8-sulfonic acid. The reversible nature of this process is evident from the fact that both quinoline and its 8-sulfonic acid yield the 6-sulfonic acid when heated at 300° with fuming sulfuric acid (67). Evidently sulfonation and desulfonation occur easily at the 8-position. The activation energy for sulfonation at the 6-position being higher, a higher temperature is required. The desulfonation of the 6-position is so difficult that sulfonation at the 6-position is irreversible. The fact that reversible substitution reactions take place makes it difficult to assess fairly halogenation reactions carried out at high temperatures.

4. Substituents

The electronic behavior of substituents in determining orientation and activation in aromatic systems has been admirably unified by Ingold, Hughes and others (79). It may be said for heterocyclic systems in general that the presence of strongly activating or deactivating substituents will largely determine the orientation of entering electrophilic groups. In the case of nucleophilic attack, however, these

species are still directed to positions alpha or gamma to the nitrogen atom.

The steric effects of substituents are often important in determining the position attacked by electrophilic species. For example, the nitration of quinoline gives mostly 5- and some 8- nitroquinoline (69). However, the nitration of 4-methylquinoline gives mostly the 8- isomer (80). Presumably the proximity of the 4-methyl group presents a steric barrier to the attack of the nitronium ion at the 5-position.

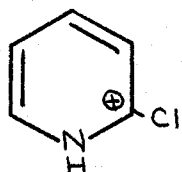
5. Catalysts

Effectively, a catalyst is an agent which by raising or lowering the activation energy for a reaction retards or accelerates the attack on the molecule. The significance of catalysis in studying the reactivity of aza-aromatic heterocycles is that such assistance can alter the orientation of the attacking species or reactivity of the molecule.

Wibaut's extensive work on the high temperature halogenation of pyridine and quinoline (81-84) reveals that as the catalyst is changed from iron (II) bromide to copper (I) bromide the orientation changes from predominantly beta to

alpha. Presumably the catalyst alters the attacking species from an electrophilic to a free radical agent (85).

The nucleophilic solvolysis of alpha- and gamma- halo compounds has been found to proceed more readily under acidic than under basic conditions. Evidence adduced by Banks (86) indicates that the protonation of the nitrogen further activates the alpha and gamma positions (XXII, XXIII).



XXII



XXIII

As might be expected, hydrogenation catalysts show varying behavior. Raney nickel in alcohol preferentially reduces the pyridinoid ring (87), whereas colloidal platinum in acetic acid leads to a completely reduced product (88).

6. Temperature

The halogenation and nitration of pyridine show a sensitivity of orientation to temperature. At 300° with vapor phase reactants the beta positions are favored. Around 500° much decomposition occurs but attack occurs

primarily at the alpha positions (80, 81). Again an explanation proposes a switch from electrophilic to radical attack (85).

The importance of temperature in case of reversible reactions such as sulfonation has already been pointed out. However, the isomer distribution in such irreversible reactions as nitration is also somewhat sensitive to the reaction temperature. An elevation in temperature will make attack at less reactive positions significantly larger.

7. Solvent

The effect of solvent for the displacement reactions in aliphatic systems has been elegantly treated by Hughes and Ingold (89). In this sense one would expect some retardation of reaction rate in electrophilic or nucleophilic reactions run in highly polar solvents. The high dielectric properties of such media should diminish the interaction of charged species.

On the other hand, the electrophilic species generated by a given reagent may largely depend upon the solvent. For example, it is felt that electrophilic chlorination may be carried on by species such as HOCl , H_2OCl^+ , Cl_2 , and Cl^+ . These species vary in reactivity and the existence of any

one of them in a solvent system depends upon the solvating and dielectric properties of the medium. As it is felt that the reactivity of an electrophilic species determines the electronic demands it will make on an aza-aromatic heterocycle, the solvent employed may influence orientation. An example of this is the nitration of quinoline. With mixed acid the products are 5- and 8- nitroquinolines. However, with lithium nitrate in acetic anhydride 3-nitroquinoline is formed in low yield (90). Previous workers reported that the 7-nitro isomer was formed (91). Acetyl nitrate is felt to be the active agent in the latter case.

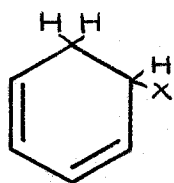
E. Chemical Properties

1. Substitution reactions

Substitution and addition reactions in aza-aromatic systems tend to overlap. It has been pointed out that a substitution reaction on an aromatic system consists in the formation of a new bond and rupture of the old bond. Such a process may occur concertedly, or there may be formed a tetrahedral intermediate of varying stability. Substitution occurs in two discrete steps. If the intermediate is sufficiently stable, it may be isolated. Subsequent elimination

of the original group may then require a distinct chemical reaction. As this intermediate is often isolable in nucleophilic attack on nitrogen heterocycles, the net result is an addition reaction, but as recovery of the aromatic system can be effected, it will be considered as substitution.

Factors contributing to the superior stability of the tetrahedral adduct in aza-aromatic systems might be considered briefly. In the case of benzene the formation of a 1,2 adduct (XXIV) should require a localization energy of 1.528β , the difference between the resonance energy of benzene and that of the butadiene-type adduct. For a 1,4 intermediate (XXV), however, the conjugation of the formal double bonds is completely disrupted and the localization energy is 2.00β .

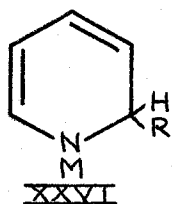


XXIV

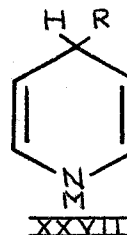


XXV

Addition of organometallic reagents ($R^{\ominus}M^{\oplus}$) to pyridine leads to 1,2 or 1,4 adducts similar to those depicted above for benzene (XXVI, XXVII).

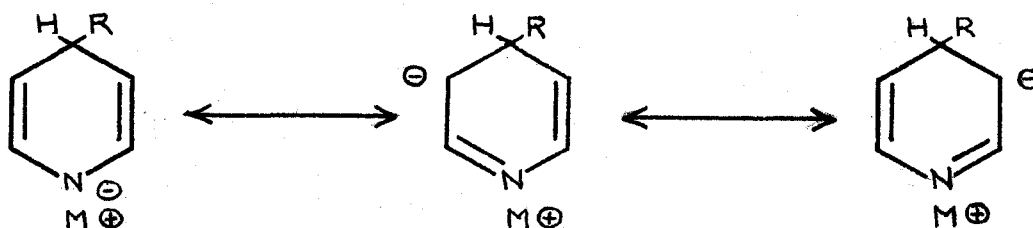


XXVI



XXVII

The localization energies for the corresponding pyridine adducts should be less than those given for the benzene molecule. When M is added to the nitrogen, this hetero atom still possesses two electrons which can occupy a p orbital. The latter orbital can overlap with the residual pi cloud, somewhat analogous to pyrrole systems. The net result is a smaller loss in resonance energy. Moreover, due to the highly polar N - M bond, the anion (XXVIII) can contribute even greater stabilization to the adduct.



XXVIII

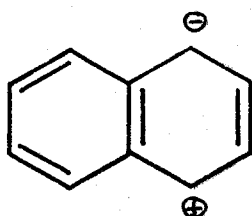
2. Electrophilic substitution

a. Nitration. The species considered as the active agent in nitration is the nitronium ion, NO_2^+ (92). Brown's study indicates that this is a very reactive electrophile of low selectivity. Although the transition state is not very close to the reactants because of the high activation energy of nitration, it seems to be sufficiently shifted

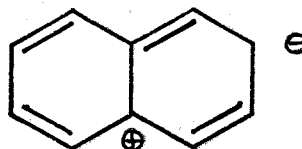
from the tetrahedral model to depend more upon the charge density and polarizability of the heterocycle's ground state.

In the series, pyridine < quinoline < isoquinoline < acridine < phenanthridine, the ease of nitration increases markedly. Pyridine gives a 22% yield of 3-nitropyridine when a solution of pyridine in 100% sulfuric acid is reacted with potassium nitrate and nitric acid at 300° (93, 94). This is contrasted with the quantitative yield of six mononitrophenanthridines obtained when phenanthridine nitrate is dissolved in concentrated sulfuric acid at 0° (13). The increasing reactivity of the benzo- and dibenzo-pyridines can be attributed to the decreasing effect of the hetero nitrogen atom on the more distant benzenoid ring. This leads to an increased polarizability at the carbon atom being nitrated. The isomers formed in the nitration of pyridine, isoquinoline and acridine are in general accord with predictions based on charge density calculations (54). Phenanthridine and quinoline, on the other hand, do not give reasonable agreement. In quinoline it is felt that the more favorable polarizability of the "alpha" positions (C₅ and C₈) partially overrides the greater charge densities at C₆ and C₃. Dewar (95) suggests that quinoline be considered as a perturbed naphthalene molecule. A valence bond approach rationalizes the greater polarizability of the "alpha"

positions in naphthalene by pointing out that structure (XXIX) has six other contributing structures, whereas structure (XXX) has only five (57).



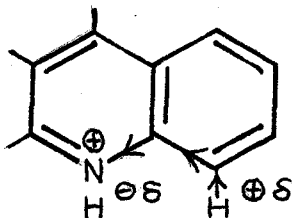
XXIX



XXX

As this enhanced polarizability facilitates nitration, the nitration of quinoline at the 5- and 8- positions is understandable. With the more reactive phenanthridine the tendency toward random substitution is seen in the formation of the 1-, 2-, 3-, 4-, 8- and 10-nitrophenanthridines (22). The predominance of the 1- and 10- isomers again can be attributed to the greater polarizability of these "alpha" positions. The charge density predictions favor electrophilic substitution in this order (54): $C_4 > C_{10} > C_8 > C_2 > C_1$, and their failure with nitration has been attributed to their closeness (24). The extremely small amount of 4-nitrophenanthridine formed may be due to the diminished polarizability of the 4-position caused by the adjacent protonated nitrogen (XXXI). This is also reflected in the smaller amount of 8-nitroquinoline and 4-nitroacridine

isolated from the nitration of quinoline and acridine, respectively (69, 96, 97).



XXXI

Nitration of these heterocycles with oxides of nitrogen (98) or a mixture of lithium nitrate and acetic anhydride (91) requires further study. Although the latter reagent was reported to give a low yield of 7-nitroquinoline, a recent communication by Dewar and Maitlis (90) claims it is really the 3-isomer. Certainly the latter isomer would seem more reasonable from charge density predictions.

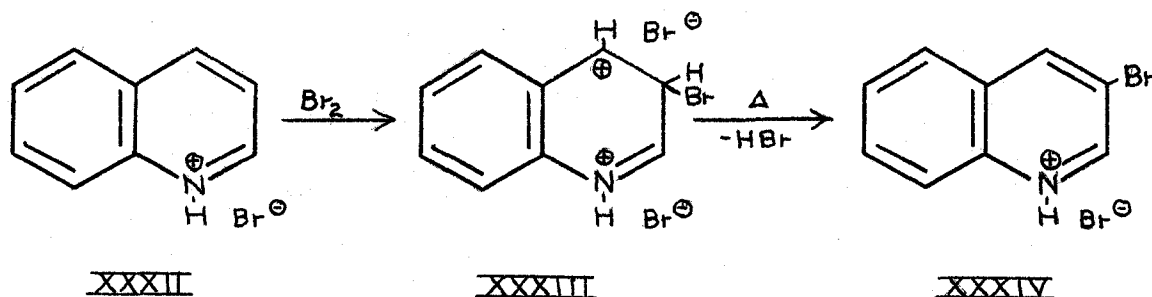
A comprehensive review of the experimental results and theoretical implications of aza-aromatic nitration has been prepared by Schofield (99).

b. Halogenation. Halogenation of aromatic systems occurring under 300° and in the presence of Lewis acids is considered to occur by an electrophilic mechanism. The intimate details of the process are not nearly as well-known as they are in the case of nitration.

Comparative data on the bromination of these nitrogen bases are quite meager. If bromination accomplished by heating the perbromide hydrobromide is examined, it appears that the facility of bromination does not vary markedly. Pyridine gives only 37% of 3-bromopyridine but also 26% of 3,5-dibromopyridine (100); quinoline yields 62% of the 3-isomer (68); and isoquinoline forms up to 74% of 4-bromoisoquinoline (101). The lack of any sharp difference in reactivity may stem from the fact that in all cases attack is on the deactivated pyridinoid ring. Acridine and phenanthridine have no available positions beta to the nitrogen in the pyridinoid ring. The position assumed by the entering bromine atom might help to elucidate the factors determining the selectivity of bromination. Bromination of acridine with N-bromosuccinimide (102) led to small amounts of two isomeric bromoacridines. The unidentified products were thought to be the 2- and 4- isomers. The analogous reaction with phenanthridine gave a 40% yield of 2-bromophenanthridine (30).

The orientation in the bromination of quinoline and isoquinoline has long been considered anomalous. As was indicated previously, charge densities would favor attack in this order: $C_8 > C_6 > C_3$ for quinoline and $C_5 > C_7 > C_8$ for isoquinoline (54). Preference of the deactivated

pyridinoid ring over the benzenoid ring suggests that there are unusual features about halogenation which require further study. It is conceivable that bromine could react with the polar $C_3 - C_4$ bond and thus halogenate the heterocycles by an addition-elimination process (XXXII-XXXIV).



The similar behavior of chlorination (103), iodination (104) and mercuriation (105) may be explicable in a parallel fashion.

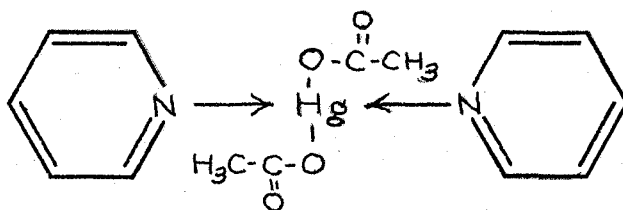
c. Sulfonation. The sulfonation of these nitrogen heterocycles results in various isomeric sulfonic acids depending upon the strength of oleum and temperature employed. The reversible nature of sulfonation, previously mentioned, complicates theoretical predictions of the most likely sites of substitution. Moreover, the reactive nature of the electrophilic sulfur (VI) oxide present in oleum tends to the formation of more isomers. Thus, the sulfonation of quinoline occurs mainly at C_8 , but C_5 , C_6 and C_7 are also attacked

(106, 107, 108). The ease of sulfonation seems to increase in the following order: pyridine < quinoline < isoquinoline < phenanthridine (109, 110). Attempts have been made to sulfonate acridine, but with limited success (111, 112).

There is evidence that the transition state of sulfonation has made much progress along reaction coordinate x in Figure 1. Melander (113) has observed that tritium-substituted aromatic systems do show a kinetic isotope effect when sulfonated. This may be interpreted to mean that the proton rupture step (XVI in Figure 1) is rate-determining. Since the transition state is much removed from the ground state, localization energies may be a better criterion for predicting sites of attack than charge densities. Pyridine can be sulfonated at the only feasible position (C_3) under rather stringent conditions. If the lower localization energy of an "alpha" position is recalled, the major attack at C_8 in quinoline, at C_5 in isoquinoline and probably C_4 in phenanthridine is understandable. The reversal of these sulfonations at more elevated temperatures demonstrates the ready accessibility of the transition state from both directions along the reaction coordinate x .

d. Mercuration. The mercuration of aza-aromatic heterocycles is usually carried out in two steps. First, the base and mercury (II) acetate are warmed to yield a

complex of two molecules of base with one molecule of the mercury salt. This is probably a Werner type complex (XXXV).



XXXV

Upon heating the complex, the heterocycle is mercurated with the elimination of acetic acid (105).

Mercuration is in general a less reactive electrophilic process than nitration or sulfonation. In its reactivity and its orientation in heterocycles, it parallels the behavior of bromination. With pyridine, quinoline and isoquinoline it attacks the same positions as does bromination. (In the case of quinoline it also attacks the 8-position.) The mercurations of acridine and phenanthridine have not been reported.

As was mentioned under the discussion of bromination, the mercuration may occur by means of an addition-elimination process.

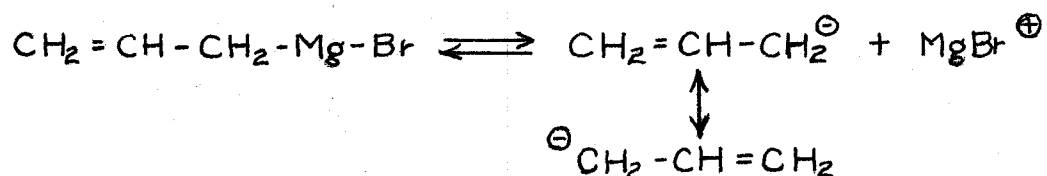
e. Friedel-Crafts alkylation. The electrophilic alkylation of these heterocyclic bases has not been accomplished. As with nitrobenzene, the aza-aromatic heterocycles fail in this reaction because of complexation of the catalyst with the hetero nitrogen atom. It is quite possible, however, that alkylation of dibenzopyridine systems could be realized under forcing conditions.

3. Nucleophilic substitution

a. Alkylation. An alkylation procedure of limited utility is the Ladenburg synthesis of alkylpyridines (114). Heating pyridine alkyl halide salts at 290-300° leads to a mixture of 2- and 4- alkylpyridines. Although the mechanism has not been studied, orientation suggests that it proceeds by a nucleophilic, or more likely, a free radical process.

Reaction of these heterocycles with Grignard reagents ordinarily has been carried out under "forcing" conditions such as the use of dioxane (115) or an autoclave (116). This illustrates the lowered nucleophilicity of ordinary Grignard reagents. It is significant that allylmagnesium bromide reacts readily with phenanthridine, acridine and quinoxaline in ether solution. The allyl anion is stabilized by

resonance and hence this Grignard reagent should have an enhanced polar character.



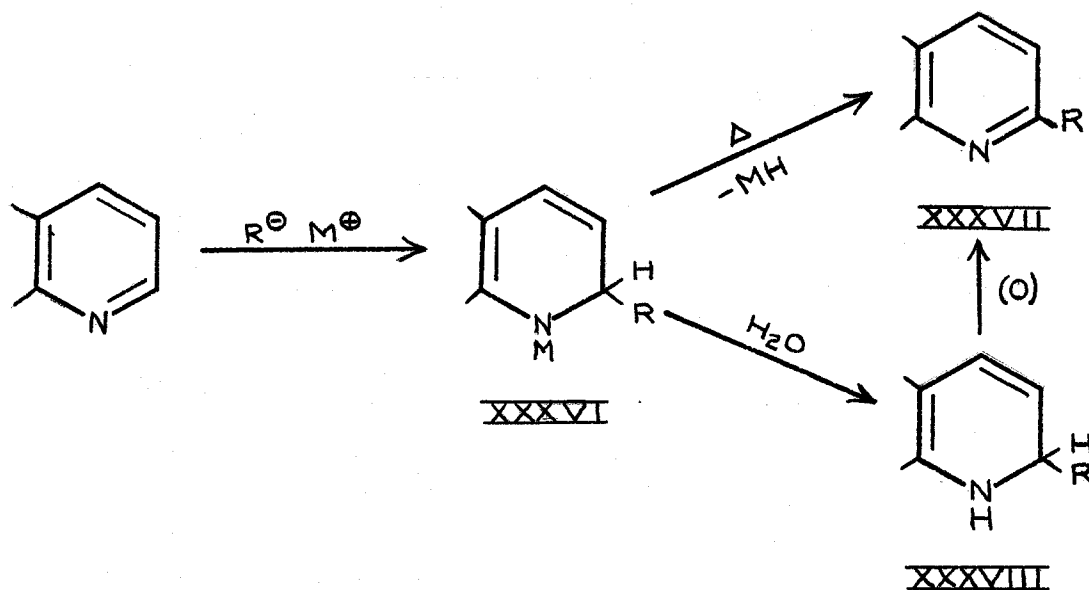
The selective character of allylmagnesium bromide versus that of *n*-butyllithium in the reaction with pyridine has been discussed previously. With a series of aza-aromatic heterocycles and anils, allylmagnesium bromide gave the following reactivity series: pyridine < quinoline \simeq isoquinoline < phenanthridine \simeq benzalaniline \simeq acridine < quinoxaline < benzophenone-anil (74).

The reaction of Grignard reagents occurs mainly at the alpha positions in quinoline, quinoxaline, isoquinoline and phenanthridine. In pyridine and acridine the gamma position is attacked. Some of the earlier work has been discredited. Although Bergmann and Rosenthal (115) reported that benzylmagnesium chloride and pyridine gave a small yield of 2-benzylpyridine, repetition of this work by Veer and St. Goldschmidt (117) led to the conclusion that the 4-isomer was formed instead. Parallel studies using allylmagnesium bromide (74) support the latter authors' work. Likewise, Bergstrom and McAllister (116) reported the preparation of

2-ethylpyridine from ethylmagnesium bromide and pyridine in an autoclave. Recently, 2-ethylpyridine was prepared unambiguously (118) and shown to differ from the product of Bergstrom and McAllister. Repetition of the autoclave reaction gave only bipyridyls (119).

The most elegant alkylation procedure involves the use of alkyllithium compounds (73). Applicable also to arylation, the reaction proceeds easily at room temperature. The series of heterocycles, pyridine, quinoline, isoquinoline, acridine and phenanthridine, all react extremely readily with n-butyllithium. The attack occurs predominantly at the alpha position, except in acridine where only the gamma position is available.

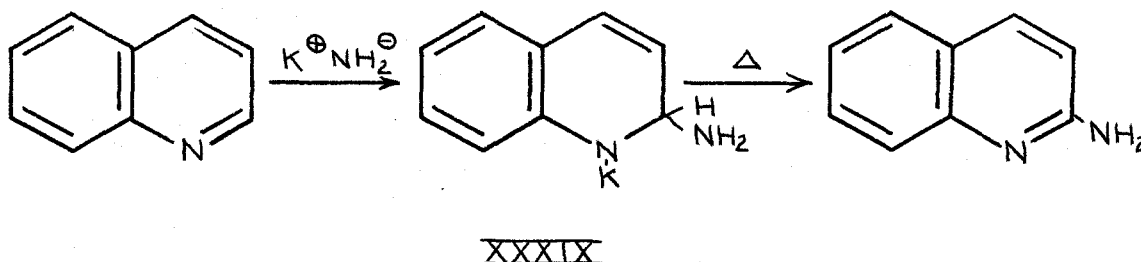
The reaction mechanism of lithium and Grignard reagents seems to involve the nucleophilic attack of the alkyl anion on the heterocycle (or heterocycle complexed with the reagent (120)) at the positions of lowest charge density. The isolable adduct (XXXVI) formed may split out the metallic hydride thermally (XXXVII), or the dihydro compound obtained upon hydrolysis may be oxidized (XXXVIII).



The factors determining the attack of allylmagnesium bromide at the gamma position of pyridine have been discussed previously. The Grignard reactions carried out under autoclave conditions may well involve free radical processes.

b. Amination. Aza-aromatic bases react readily with potassium amide to yield amino derivatives with the evolution of hydrogen (121). With pyridine and quinoline both the alpha and gamma derivatives are formed. There seems to be no marked difference in yield among pyridine (82-90%), quinoline (63%), isoquinoline (83%), phenanthridine (90%) and acridine (72%). Data indicate that this process is a nucleophilic attack of the amide anion on the positions of lowest charge density with the expulsion of the hydride ion.

The process is thus quite analogous to nucleophilic alkylation.



Bergstrom (122) has obtained experimental evidence for the intermediate adduct (XXXIX).

The amide ion is a reactive nucleophile, but less reactive than the hydride or alkyl anion.

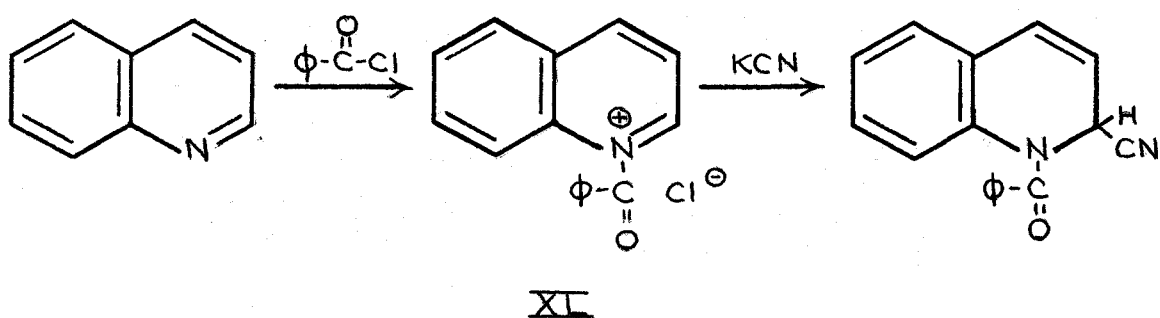
c. Hydride ion reduction. The behavior of a series of aza-aromatic heterocycles towards lithium aluminum hydride has been studied recently by Bohlmann (123). Although no quantitative data were presented, facility of reaction increased in the order: pyridine < quinoline < quinoxaline < acridine. Interestingly enough, piperidine was formed in 10% yield from pyridine, together with an unstable product behaving like 1,2-dihydropyridine. The product from quinoline was possibly a mixture of 1,2- and 1,4-dihydropyridines, as two distinct orange-red picrates were isolated. The behavior of phenanthridine with this reagent has been studied independently (124) and 5,6-dihydrophenanthridine was

obtained in 74% yield. These data also suggest a dependence of reactivity on the lowered charge density of the alpha and gamma positions, as reaction occurs through a nucleophilic attack of the hydride ion. The behavior of lithium aluminum hydride is quite analogous to that of n-butyllithium although it seems to be less reactive.

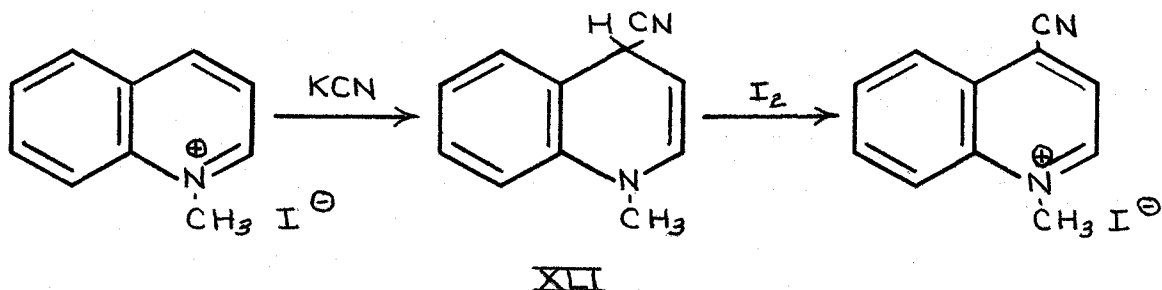
d. Hydroxylation. The nucleophilic hydroxylation of these nitrogen bases by dry potassium hydroxide was discovered by Chichibabin (27). Recently, the reaction was extended to phenanthridine. Analogous to amination, hydroxylation occurs through a nucleophilic attack of the hydroxide ion at a position of lowered charge density. The large activation energy of the process is reflected in the high temperatures required (200-300°). Amination and hydroxylation probably have as their rate-determining step the expulsion of the hydride ion. The C-H bond energy is 87.3 kilocalories per mole, whereas that of a C-N and a C-O bond is 48.6 and 70.0 kilocalories per mole, respectively (125). Judged by the time and temperature, the facility of hydroxylation increases thus: pyridine < quinoline < isoquinoline < phenanthridine. Reaction takes place uniformly at the alpha position.

e. Cyanation. Various procedures lead to the nucleophilic attack of cyanide ion on these heterocycles. A general procedure developed by Reissert (126) has been

applied to quinoline, isoquinoline and phenanthridine (127), but fails with pyridine (128). The procedure involves the reaction of potassium cyanide with the benzoyl chloride complex (XL) of the heterocycles in anhydrous solvents.



The reaction proceeds readily and the cyanide ion attacks the alpha position. This is to be contrasted with the Kaufmann reaction (129) in which treatment of quinoline methiodide with potassium cyanide leads to a dihydro intermediate (XLI) oxidizable by iodine to 4-cyanoquinoline methiodide.



Surely attack at either the alpha or gamma position in quino-
line is compatible with nucleophilic cyanation, but the
switch in orientation must be considered. The fact that the
benzoyl chloride complexes of heterocyclic bases may be used
as benzoylating agents (130) suggests a loosely bound com-
plex on the nitrogen (XL). On the other hand, methiodides
of heterocyclic bases are not methylating agents under
ordinary circumstances. This points to a methyl group in-
timately bound to the nitrogen. Such a group could create
a definite steric barrier to attack at the alpha position,
whereas the benzoyl chloride complex might be loose enough
to permit access to the alpha position.

Finally, acridine reacts readily with hydrocyanic acid
in alcohol to give 9-cyanoacridine (131). Examination of
the experimental conditions reveals that the cyanide ion, a
rather unreactive nucleophile, requires activation of the
heterocycle by quaternization of the nitrogen atom. With
the more reactive acridine system such activation is
unnecessary.

4. Free radical substitution

Admittedly much less is known about the intricacies of
free radical attack (132). However, such processes seem to

be involved in surface reactions (catalytic hydrogenation and metal reductions), very high temperature reactions (vapor phase bromination at 500°), and in reactions involving metals or radical sources (sodium metal or peroxides).

a. Phenylation. If the polarizability of a position is important, the alpha and the gamma positions should be preferred in radical processes (70). Experiment partially confirms this. When pyridine is phenylated by radicals from benzoyl peroxide or basic benzene diazonium salts (133), all three phenylpyridines are isolated but predominantly the alpha isomer. The reactivity of the phenyl radical may cause a tendency toward random substitution.

b. Methylation. Recently, Levy and Szwarc (134) carried out a quantitative study of the interaction between aromatic systems and methyl radicals obtained from the decomposition of acetyl peroxide. No attempt was made to determine the orientation of the methyl groups in the products. Instead, the aromatic systems were assigned relative reactivities towards methyl radicals with benzene taken as unity. The values in Table 2 were obtained. In general, the aza-aromatic heterocycle is more reactive than its parent carbocycle, but acridine is anomalous in this respect. It was observed that there was a linear relation between the

Table 2. Relative reactivities of aromatic systems toward methyl radicals

(Benzene taken as 1)

Carbocycle	Reactivity Index	Heterocycle	Reactivity Index
naphthalene	22	pyridine	3
phenanthrene	27	quinoline	29
chrysene	58	isoquinoline	30
pyrene	125	acridine	430
anthracene	820		

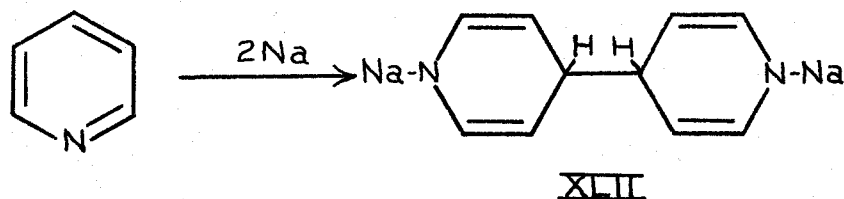
logarithm of the methyl affinities and the singlet-triplet excitation energies of the aromatic systems.

c. Reduction. This discussion embraces those reductions involving a metal coupled with an acid or a base. Modern opinion considers as fiction the importance of "nascent" hydrogen in such reductions. Burton and Ingold (135) have pictured such reductions as occurring on the metal surface as free-radical or nucleophilic transfer of electrons to the pi-cloud of the electrophilic molecule. With nitrogen heterocycles the electron-receptive centers would be the alpha and gamma positions. The anion formed

will accept protons from the solvent at the position of highest charge density. The pyridinoid ring, once partially disrupted in this manner, tends to be completely reduced. This occurs despite the fact that the hetero ring should be more resonance-stabilized than the benzenoid ring. For a lucid consideration of such non-thermodynamic reductions, the discussion of Hammond (76) should be read.

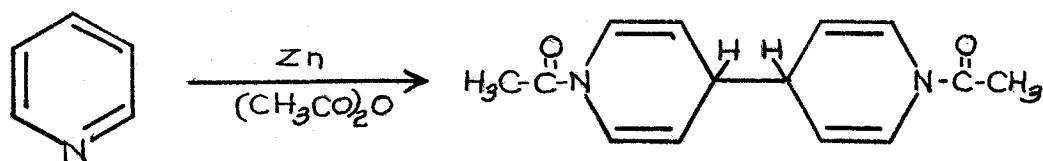
Sodium and alcohol, and tin and hydrochloric acid form piperidine, 1,2,3,4-tetrahydro-quinoline and-isoquinoline from the respective heterocycles (136-138). Acridine and phenanthridine are reduced to 9,10-dihydroacridan (139) and 5,6-dihydrophenanthridine (140), respectively.

d. Coupling. The use of active metals as reducing agents for these heterocycles has led frequently to bi-molecular reduction. In the aldehyde analogy of Bergstrom this is equivalent to the pinacol reduction. The reaction occurs with pyridine (141), quinoline (142), acridine (143) and derivatives of isoquinoline (144), but it has not been reported for phenanthridine. At room temperature pyridine seems to couple mainly through the gamma positions (XLII), and to a lesser extent through the alpha positions.



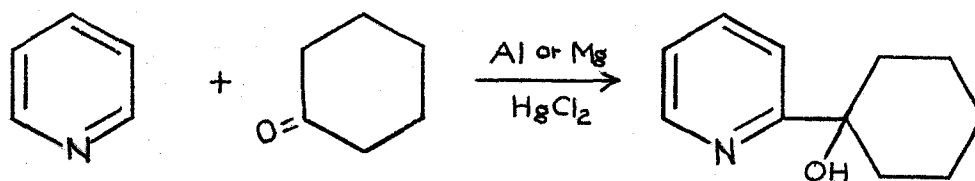
Presumably such coupling occurs on the metal surface by free radical processes. At higher temperatures 2,3', 3,3' and 3,4' coupling products are also formed, besides polypyridyls (145). The behavior of quinoline is different as it forms mainly the 2,3' coupling product (142). Acridine yields 9,9'-biacridyl (143).

An interesting reaction discovered by Dimroth (146) and extended by Wibaut and Arens (147) is the reductive coupling of pyridine with zinc and acetic anhydride.



The conditions suggest that the acetylpyridinium ions are reduced on the zinc surface by a simultaneous two electron transfer, analogous to the pinacol reduction.

Work by Emmett and coworkers (148) has led to a mixed pinacol reduction with pyridine and aliphatic ketones. The predominant product is the 2- isomer (XLIII), although the amount of the 4-isomer is sometimes significant (149).



XLIII

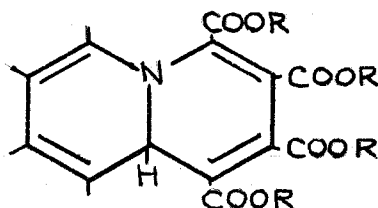
e. High temperature reactions. Reactions occurring under stringent conditions of heat and pressure tend to favor radical processes. It has been mentioned that vapor phase bromination (81-84) and coupling (150) indicate that free radical processes are operative.

5. Addition reactions

a. Hydrogenation. Catalytic hydrogenation of these nitrogen bases may occur selectively in the pyridinoid ring. For example, Raney nickel reduction of pyridine (151), quinoline (87) and isoquinoline (152) leads to piperidine, 1,2,3,4-tetrahydro-quinoline and -isoquinoline, respectively. Under these conditions acridine yields acridan (153) and phenanthridine forms 5,6-dihydrophenanthridine (140). With platinum and glacial acetic acid the aza-aromatic heterocycles tend to be completely reduced (88). The greater tendency of the pyridinoid ring to reduction may be

attributed to its greater electrophilicity when adsorbed on the metal surface.

b. Reaction with dialkyl acetylenedicarboxylate. A rather peculiar reaction is undergone by dialkyl acetylenedicarboxylate and pyridine (154), quinoline (155), isoquinoline (156) or phenanthridine (157). Although several labile adducts have been isolated, the accepted structure of the stable adduct is represented as (XLIV).



XLIV

Analogous to anthracene, acridine undergoes a normal Diels-Alder reaction as no alpha position is available (158). The mechanisms of these reactions are not clear, but it is possible that radical processes determine preference for the alpha and gamma positions.

c. Nitrogen complexes. Acceptance of the unshared sp^2 electrons on the hetero atom by an atom or cation tends to increase the nitrogen's effective electronegativity.

The resultant effect on the charge density has been considered previously.

1) N-Oxides. The action of peracids on these nitrogen heterocycles leads to the formation of N-oxides. Careful studies on the ease of formation have not been made, but the action of hydrogen peroxide in acetic acid suggests that phenanthridine may be more difficult to oxidize than quinoline or pyridine (159). In the former case phenanthridone is formed as a by-product (160). This increased resistance may be due to the lower basicity of phenanthridine.

ii) Quaternization. The reaction with alkyl halides or dialkyl sulfates occurs with a notable variation in facility. Methyl iodide reacts readily with pyridine, quinoline and isoquinoline, but acridine and phenanthridine require heating in hot nitrobenzene or benzene for quaternization. As the calculated electron density on the nitrogen increases from pyridine to acridine, one would expect acridine to be more reactive than pyridine. Parallel studies with the quaternization of tertiary alkyl amines show that there is a marked dependence of activation energy on the basicity of the amine (161). The lowered reactivity of phenanthridine can be owed to its weak basicity, but not that of acridine (Table 3).

iii) Salt formation. The unshared electron pair on the nitrogen can accept a wide variety of Lewis acids, ranging from protons to aluminum chloride. The basicity of these heterocycles toward protons has been of considerable theoretical and physiological interest. Expressed in terms of pK_a for the equilibrium,



$$K_a = \frac{[B][H^{\oplus}]}{[BH^{\oplus}]}$$

the values are given in Table 3 (162). The decrease in

Table 3. pK_a Values for heterocyclic bases at 20°

Base	pK_a in H_2O	pK_a in 50% EtOH
pyridine	5.23	--
isoquinoline	5.14	--
quinoline	4.94	--
acridine	5.60	4.11
phenanthridine	--	3.30

basicity in going from pyridine to phenanthridine is opposed to predictions based on charge densities (54). Dyatkina (163) suggests that a change in the C-N resonance integral may be the source of this discrepancy, and Brown and Dewar (59) feel that second order terms involving the self-polarizability of the nitrogen atom may be important.

The pK_a values of certain diaza-aromatic heterocycles are presented in Table 4 (162). Introduction of a second nitrogen atom greatly reduces the base strength.

Table 4. pK_a Values of diaza-aromatic heterocycles at 25°

Base	pK_a
quinazoline	3.51
phthalazine	3.47
cinnoline	2.70
pyridazine	2.33
pyrimidine	1.30
phenazine	1.23
quinoxaline	0.8
pyrazine	0.60

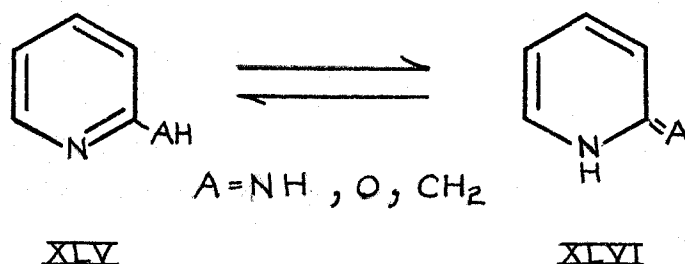
6. Ring stability

The thermal stability of these nitrogen heterocycles is reflected in their recovery from the pyrolytic products of soft coal. Both acridine and phenanthridine distil unchanged at around 350°.

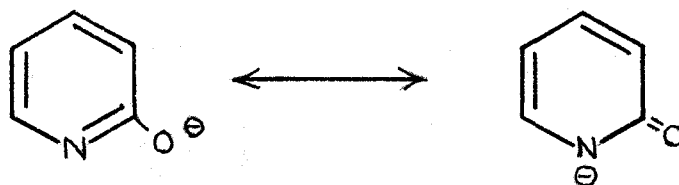
Oxidation of these bases with alkaline potassium permanganate seems to show the superior stability of the pyridinoid ring. The resistance of pyridine to oxidation makes it a suitable solvent for oxidation reactions. With quinoline the benzenoid ring is preferentially destroyed, yielding pyridine-2,3-dicarboxylic acid. Isoquinoline is also attacked in the benzenoid ring leading to pyridine-3,4-dicarboxylic acid. Acridine is degraded to quinoline-2,3-dicarboxylic acid. Degradation studies of substituted phenanthridines have yielded phthalic acid (24) but the products from phenanthridine itself have not been reported. The general preservation of the pyridinoid ring may be due to its superior resonance stabilization. The nature of the attack is somewhat dependent upon the oxidizing agent employed, however.

7. Comparison of characteristic derivatives

The characteristic behavior of the alpha and gamma derivatives of these heterocycles warrants careful examination. Experimental evidence in the case of the amino, methyl and hydroxyl derivatives has suggested the possibility of tautomerism (XLV, XLVI).



Many researchers have attempted to determine chemically which tautomer is more descriptive of the real state of the molecule. Thus, workers have methylated 2-hydroxypyridine with dimethyl sulfate in basic solution and also with diazomethane. Since the first reagent gave N-methyl-2-pyridone and the second 2-methoxypyridine, it was felt that tautomer (XLVI) is more important in basic solution and that tautomer (XLV) predominates in neutral solution (164, 165). Such evidence is of no validity, since in basic solution one is really dealing with the anion (XLVII).



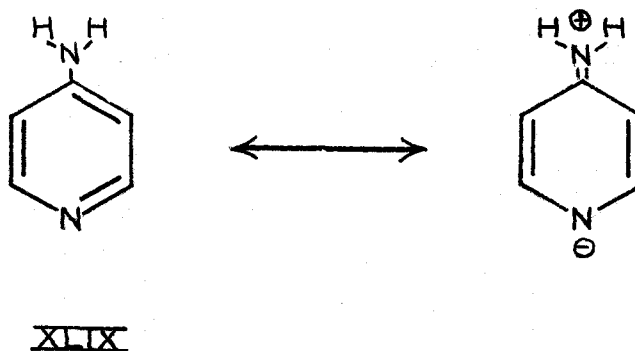
XLVII

The point at which methylation will occur then depends upon how much the anion is deformed in the course of reaction. If little deformation is necessary, the site of highest charge density will be methylated. If much deformation is necessary, the site causing the lesser loss of delocalization energy will be attacked. These considerations stress the unreliability of using chemical methods only to study tautomeric systems.

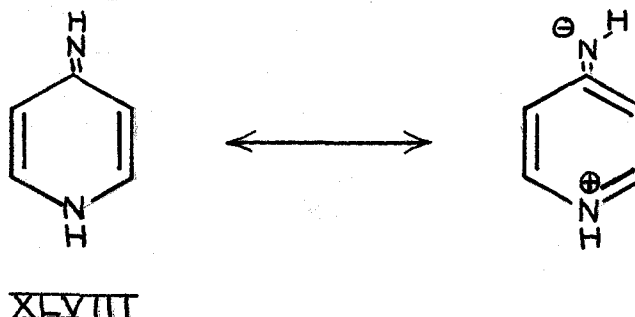
a. Amino derivatives. The position of the possible tautomeric equilibrium between the alpha and gamma amino tautomer and the imino form has been studied by both chemical and physical means. Besides alkylation experiments similar to those carried out with 2-hydroxypyridine, the behavior of these amines upon diazotization, hydrolysis and attempted Schiff base formation has been adduced as proof for the existence of one or the other tautomer. All this chemical evidence is subject to objection, as a chemical reaction perturbs the system a great deal. If one tautomer reacts more readily, the existence of a mobile equilibrium will

allow the more reactive form to be replenished at the expense of the less reactive one.

Even the physical methods of studying such tautomerism yield ambiguous results in certain instances. Leis and Curran (166) measured the dipole moment of 4-aminopyridine and compared it with that of aniline and pyridine. They ruled out the imino form (XLVIII) in favor of the amino form (XLIX) as they felt the former could not account for the high dipole moment.

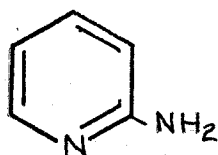
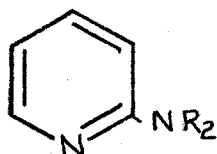
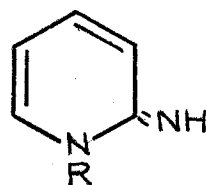


Angyal and Angyal (167) argued, however, that this conclusion did not follow of necessity, as the imino form could have significant dipolar character.

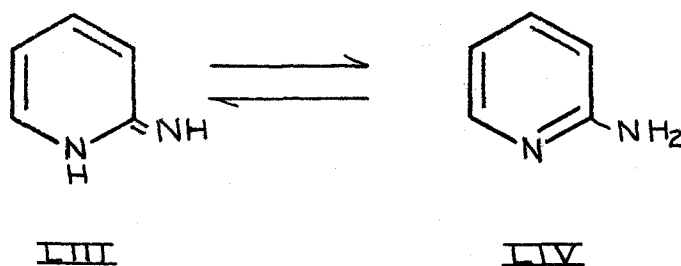


That imines can have high moments was demonstrated by the value obtained from 1,4-dihydro-4-imino-1-methylquinoline (5.1D), as compared with that of 4-aminoquinoline (4.4D).

The observation of the shifts obtained in the ultraviolet spectra of amino-pyridines, -quinolines and -isoquinolines in acidic and basic solutions led Steck and Ewing (168) to state that the alpha and gamma amino derivatives existed in the imine form. This conclusion was based upon the assumption that nuclear protonation should cause a bathochromic shift, whereas protonation of the amino group should cause a hypsochromic shift in the ultraviolet spectra. Since there was little appreciable bathochromic shift of the amines' spectra in acid solution, it was concluded that the hetero nitrogen was largely saturated. The pitfalls of conclusions from spectral shifts are discussed in a careful fashion by Angyal and Angyal (167). A more reliable criterion is that of the similarity of the amines' spectra with that of N-methylated derivatives. Such a comparison was carried out by Anderson and Seeger (169) with the 2- and 4-aminopyridines. The close similarity of the spectrum of 2-aminopyridine (L) with that of 2-methylamino- and 2-dimethylaminopyridines (LI), and its dissimilarity to N-methylpyridonimine (LII) indicate that 2-aminopyridine is in the amino form.

IIIIII

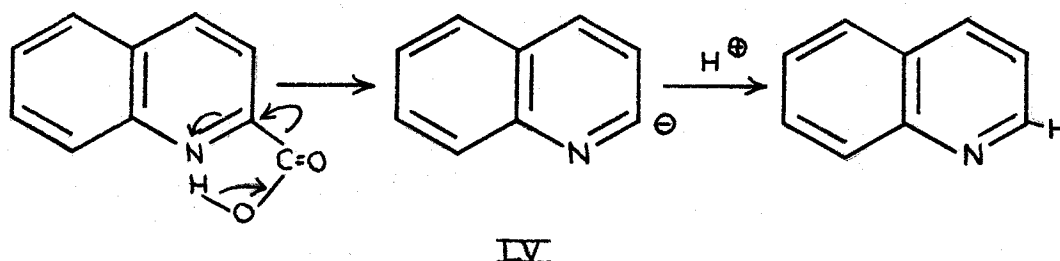
Moreover, no evidence could be obtained for any tautomeric equilibrium. The same conclusions were reached with 4-aminopyridine. Angyal and Angyal (167) calculated that the equilibrium constant for the tautomeric system (LIII, LIV) is



$$K_{\text{taut}} = \frac{[A]}{[I]} = \frac{K_a(\text{amine})}{K_a(\text{imine})} = 10^3$$

The loss in aromatic resonance in going from the amine to the imine was 4.5 kilocalories per mole. K_a (imine) was estimated by using the K_a of N-methylpyridonimine. By examination of existing evidence these authors felt that the amino form was also the more stable form with the corresponding amines of quinoline, isoquinoline, acridine and phenanthridine.

b. Carboxylic acids. The characteristic tendency of alpha and gamma carboxylic acids to undergo thermal decarboxylation has been compared with the instability of alpha keto acids. The mechanistic studies of Hammick (170, 171) on the decarboxylation of quinoline-2-carboxylic acid strongly support the following mechanism.



That an intermediate anion (LV) is involved is indicated by the products isolated when carbonyl compounds, quinoline or m-dinitrobenzene is present during decarboxylation. The long lifetime of this anion is due to the stabilizing effect of the diminished charge density at the alpha position. The stabilization is certainly not through resonance delocalization, as the anion is in an sp^2 orbital which is orthogonal to the pi cloud. More likely, it is a direct inductive effect along the sigma bonds toward the nitrogen.

Careful studies on the ease of decarboxylation of alpha- and gamma-carboxylic acids have not been carried out.

However, pyridine-2,3-dicarboxylic acid decomposes around 230° into nicotinic acid, quinoline-2-carboxylic acid decarboxylates above its melting point (158°) and isoquinoline-1-carboxylic acid decomposes at 161° . Simply heating phenanthridine-6-carboxylic acid to 150° brings about smooth conversion to phenanthridine (21). Gamma acids usually require a higher temperature for decarboxylation. Acridine-9-carboxylic acid yields acridine when heated at 295° for a short time (131).

c. Dihydro derivatives. Reduction of heterocyclic bases or the addition of organometallic reagents to the pyridinoid ring leads to dihydro derivatives. As one passes up the series, pyridine < quinoline \approx isoquinoline < acridine \approx phenanthridine, the stability of the dihydro derivative shows a definite increase. With pyridine it seems that 1,4-dihydro derivatives may be more stable chemically than 1,2-dihydro compounds. The former are the products isolated from the Hantzsch pyridine synthesis (77) and react sluggishly with silver nitrate (172). 1,2-Dihydropyridines are obtained from the alkylation of pyridine with alkyllithium compounds (73), and react readily with silver nitrate (172).

These dihydropyridines together with those of quinoline and isoquinoline are readily oxidized in air and are difficult

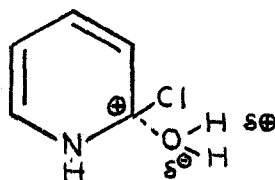
to isolate. On the other hand, acridine (139) and phenanthridine (140) can be converted to fairly stable dihydro products. The increase in the stability of dihydro derivatives of polycyclic systems may be attributed to the decrease in localization energies.

d. Halogen derivatives. Halogens located alpha and gamma to the hetero nitrogen are prone to nucleophilic displacement by such reagents as water, alcohols, phenols, sulfides and amines (173). Although Chapman and his group (174, 175) have compared halonitrobenzenes with halopyridines by kinetic studies, only qualitative comparisons have been made among halo derivatives of aza-aromatic heterocycles. Bradlow and Vanderwerf (176) studied the hydrolysis of various halo pyridines by heating them with dilute hydrochloric acid. alpha-Fluoropyridine underwent hydrolysis, whereas the corresponding chloro and bromo derivatives did not. Since 2-chloroquinoline did hydrolyze, it was more reactive than the corresponding pyridine compound. The enhanced reactivity of gamma halopyridines has been attributed to the stability of the tetrahedral transition state. By Waters' quinoid hypothesis (177) such a para structure would be more stable than the ortho form (alpha position).

Comparison of the halo derivatives of pyridine, quinoline, isoquinoline, phenanthridine and acridine shows that

the ease of solvolysis increases in the same order. Strikingly enough, 9-chloroacridines and 6-chlorophenanthridines are so prone to solvolysis under neutral or acidic conditions that attempted recrystallization from ethanol leads to extensive conversion to acridones and phenanthridones, respectively. Halo derivatives of di- and triaza-aromatic heterocycles show an even greater reactivity. The presence of additional hetero nitrogens further decreases the electron density at the alpha positions (178).

Since water and ethanol are nucleophiles of moderate reactivity, it is reasonable to represent the transition state as close to the tetrahedral model (LVI).



LVI

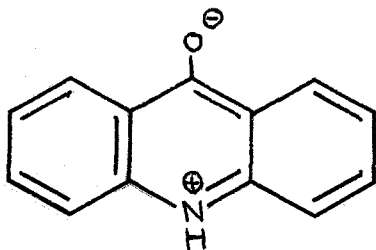
The increased reactivity of halo-phenanthridines and -acridines can then be related to their lower localization energies.

e. Hydroxyl derivatives. The nature of the tautomeric equilibrium for hydroxyl compounds has been given careful

study by many workers. 2-Hydroxypyridine can undergo O- or N-methylation depending upon conditions. Ultraviolet absorption studies in acidic and basic solutions have been compared with N-methylpyridone and with 2-methoxypyridine, respectively. The resemblance of spectral curves seems to indicate that in neutral or acid solution 2-hydroxypyridine is predominantly in the pyridone form. Similar data were obtained from 4-hydroxypyridine (179).

On the other hand, 2- and 4-hydroxyquinolines do not show appreciable spectral shifts in solutions of any pH. It was concluded from this that the quinolone tautomer is the more stable form (180). As with the amine-imine tautomeric system, more satisfactory evidence lies in the spectral similarities of carbostyryl and N-methylquinolone (181).

The infrared spectra of acridone and phenanthridone have pronounced carbonyl bands at 6.1μ and imine bands at 3.1μ . These compounds therefore seem to be cyclic amides. Moreover, only N-methylation has been accomplished. Albert has explained the extreme stability of acridone in terms of "dipolar resonance" contribution (182) (LVII).

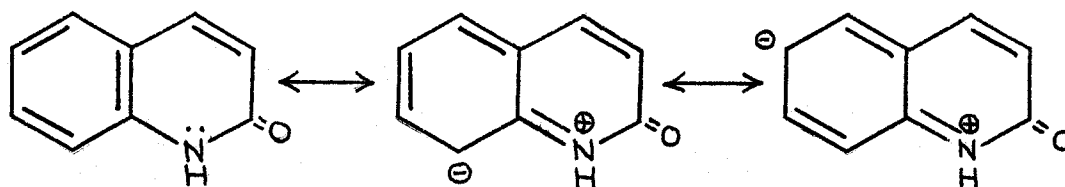


LVI

A molecular orbital approach would simply take cognizance of the pi-pi interactions possible between the oxygen and C₉ and the nitrogen and the aromatic pi-cloud.

Thus, it seems that the ketonic tautomer becomes progressively more stable as one goes from pyridones to acridone (51).

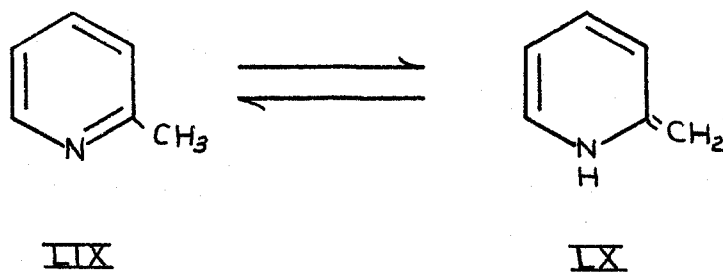
The substitutional chemistry of these derivatives is interesting since they are prone to electrophilic attack in the benzenoid ring ortho and para to the NH group. This is in accord with a neutral group having unshared electrons adjacent to the benzene ring (78) (LVIII).



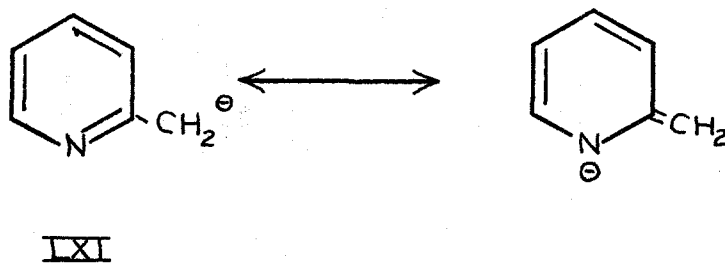
LVIII

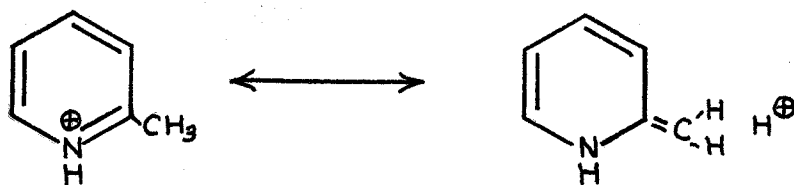
Thus, carbostyryl is nitrated in the 6- and 8-positions (183); acridone is sulfonated (184) and nitrated in the 2- and 4-positions (111, 112); and phenanthridone is nitrated in the 2- and 4-positions (22, 185) and halogenated in the 2- position (186).

f. Methyl derivatives. Derivatives having methyl groups alpha and gamma to the nitrogen may be considered as methylketone ethers in the ammonia analogy of Bergstrom. The chemical reactions of such methyl derivatives include halogenation, oxidation, alkylation and condensation with carbonyl and nitroso reagents (28). The lability of the hydrogens has been explained in terms of a possible tautomeric equilibrium (LIX, LX).



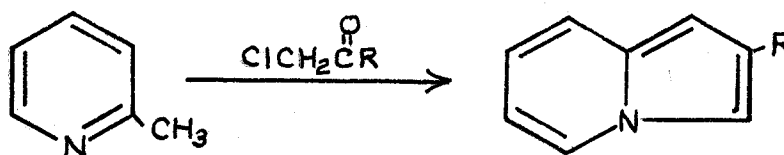
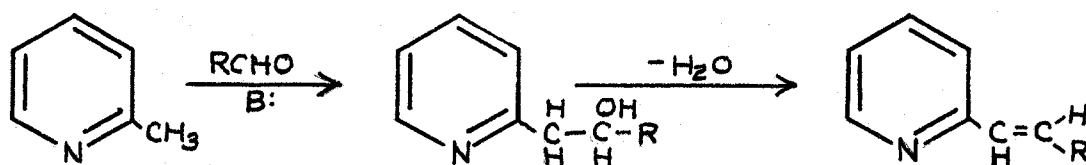
However, infrared data do not support the presence of much imino form (187). Either the anion (LXI) or cation (LXII), formed by the abstraction or addition of a proton, respectively, are resonance stabilized. This stabilization of the charged species should increase both the acidity of the methyl hydrogens and the basicity of the hetero nitrogen.



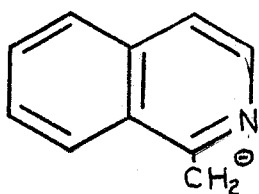


LXII

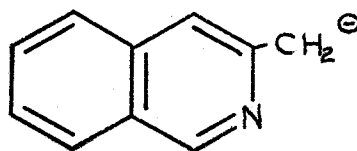
Hence, the behavior of the alpha and gamma methyl derivatives is markedly dependent upon the basicity or acidity of the system. As stressed previously, the subsequent chemical reactions will not depend so much upon which tautomer predominates, as they will upon the electronic demands of the reagent used. Chemical behavior tends to support this interpretation:



In rationalizing the superior reactivity of 1-methylisoquinoline over that of 3-methylisoquinoline Gensler (152) points out that the anion (LXIII) formed in base-catalyzed condensations has a greater stability due to resonance delocalization than anion (LXIV).



LXIII

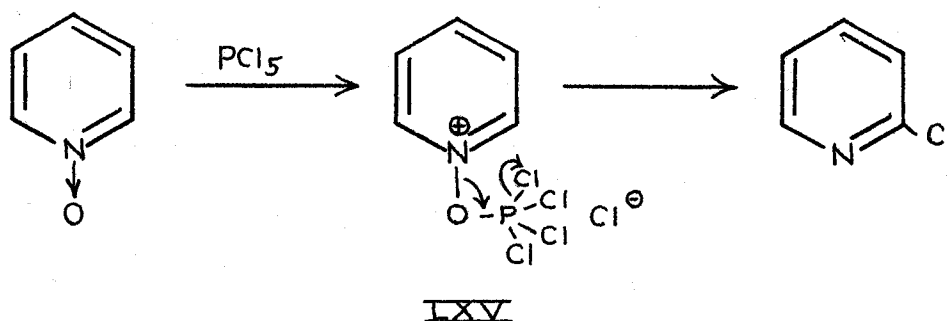


LXIV

Consequently, if the base-catalyzed condensations of these methyl compounds with aldehydes depend on the presence of the anion, Gensler's argument could be extended to azaromatic heterocycles in general. If one counts the resonance structures stabilizing the anion and assumes that the larger the number, the more stable the anion, one obtains a series of methyl anions of increasing stability. Thus, as one passes up the series, 2- and 4- methylpyridines < 2-methylquinoline \simeq 4-methylquinoline < 1-methylisoquinoline < 6-methylphenanthridine \simeq 9-methylacridine, the anion should become increasingly more stable. One would expect

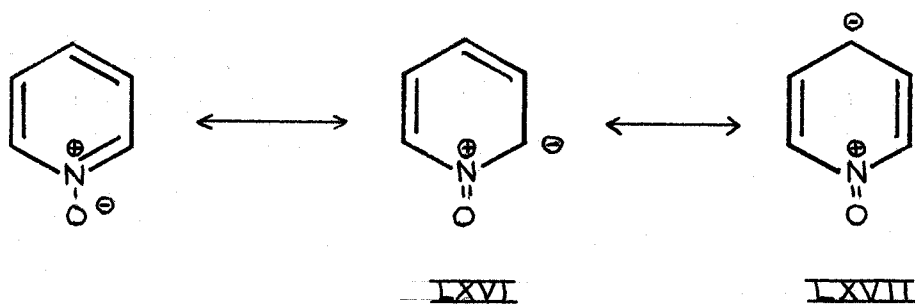
both the acidity of the methyl hydrogens and the ease of base-catalyzed condensation to increase in this order.

g. N-Oxides. The enhanced reactivity of the alpha and gamma positions in N-complexes has already been discussed. Here will be considered the characteristic reaction of N-oxides. Interaction with such nucleophilic reagents as phosphorus (V) chloride (LXV), potassium cyanide and Grignard reagents leads to removal of the oxygen and attack at the alpha or gamma position (188).



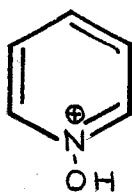
Of great theoretical interest has been the behavior of pyridine-1-oxide with nitric acid. Contrary to expectations this reagent leads to an excellent yield of 4-nitropyridine-1-oxide (159). Both the facility and orientation of this nitration are surprising, as the orientation would suggest a nucleophilic attack by nitric acid. However, a valence

bond description of pyridine-1-oxide shows the unshared electron pairs on the oxygen can overlap with the pi-cloud (LXVI, LXVII).



Dipole moment data are in accord with such charge separation (189). Nitration can thus occur electrophilically at the 4-position which has an enhanced charge density and polarizability.

Recently Mosher and Welch (190) have attempted the sulfonation and bromination of pyridine-1-oxide. Sulfonation occurred at the 3-position and no bromination could be effected. In fuming sulfuric acid the oxygen is probably extensively protonated (LXVIII).



LXVIII

and thus the activating influence of the oxygen is diminished. Consequently, orientation would again resemble that of pyridine. Recently, the mercuration of pyridine-1-oxide at the 4-position was reported (191).

The behavior of acridine-10-oxide and phenanthridine-5-oxide toward nucleophilic reagents parallels that of other oxides. Attack occurs at the free alpha or gamma position, respectively.

F. Physical Properties

1. Molecular dimensions

As aza-aromatic heterocycles are derived formally from the parent carbocycles by substituting CH by N, the similarity in bond lengths and bond angles is not surprising. The regular hexagonal configuration of benzene is confirmed by studies of the vibration-rotation spectrum (192). Electron diffraction measurements of bond lengths in benzene gave $1.39 \pm 0.02 \text{ \AA}$ for C-C and $1.08 \pm 0.04 \text{ \AA}$ for C-H. Parallel measurements on the pyridine molecule showed the same dimensions for the C-C and C-H bond lengths within experimental error, and gave a value of $1.37 \pm 0.03 \text{ \AA}$ for the C-N bond length (193). In the light of a recent measurement of

pyridine's dipole moment by microwave spectroscopy, however, DeMore, Wilcox and Goldstein (65) suggested the following parameters: $C-N = 1.35 - 1.36 \text{ \AA}$; $C-C = 1.39 \text{ \AA}$; $C-H = 1.08 \text{ \AA}$; and the angle $CNC = 114-117^\circ$. Such a narrowed molecule is in better agreement with the data obtained.

The dimensions of other aza-aromatic heterocycles will probably be quite similar to those of the parent carbocycle. One may expect a short C-N bond throughout this series of heterocycles due to the polar nature of the bond. As in the case of carbocycles, the C-C and C-N bond lengths in these heterocycles should be related to their multiplicity. In the sense of Pauling (125) bond multiplicity is a measure of the "double-bond character" of a C-C bond. A high bond multiplicity for a C-C bond means that it is represented more frequently as a $C=C$ in the valence bond structures of the resonance hybrid. Such a bond will be shorter and will tend to resemble an olefinic bond in chemical behavior. Double-bond reactions such as osmium tetroxide oxidation, ozonization and argentation (complexation with silver ion) seem to occur at bonds of high multiplicity (51, 194).

2. Molar refraction

The polarizability of a molecule depends upon the displacement of electrons by an electric field and is measured

by the molar refraction. Early attempts to set up a system of atomic refraction constants and thus to calculate the molar refraction of a compound a priori failed with unsaturated systems. Conjugated molecules gave experimental values higher than calculations would predict. In the modern view of conjugation these exaltations are understandable as they imply a greater electronic polarizability. The delocalization of pi electrons in conjugated systems not only lowers the energy of the molecule's ground state, but decreases the lower lying levels of the excited states even more. The net result is a decrease in electronic excitation energy and an increase in polarizability as the conjugated system is extended (compare section on "Ultraviolet spectra"). This explains why deviations (exaltations) from values obtained by atomic and group refraction constants become more pronounced as one goes to polycyclic systems. This is shown by the aza-aromatic heterocycles in Table 5 (195, 196). Instead of the use of empirical refraction constants a modern treatment of condensed aromatic systems has taken account of the high mobility of the pi electrons and the planarity of the ring system. With these calculations the discrepancy between experimental and predicted molar refractions is significantly smaller (Table 6) (197).

Table 5. Molar refractions of aza-aromatic heterocycles and their exaltations from calculated values

Heterocycle	M.R. (found)	M.R. (calc.)	Δ M.R.
pyridine	24.02	25.16	-1.14
isoquinoline	41.41	40.49	0.92
quinoline	41.83	40.49	1.34
acridine	62.34	55.83	6.51

Table 6. Molar refractions of condensed aromatic systems and their exaltations from calculated values

Compound	M.R. (found)	M.R. (calc.)	Δ M.R.
benzene	26.2	26.2	0.0
naphthalene	44.1	43.5	0.6
anthracene	65.4	62.0	3.4
phenanthrene	62.3	62.0	0.3
pyrene	74.0	70.8	3.2
isoquinoline	41.6	41.5	0.1
quinoline	41.8	41.5	0.3
acridine	64.3	60.2	4.1

Referring to the aromatic systems in Table 6, one can see that the molar refraction, and hence the mean polarizability, of a given heterocycle is less than that of the parent carbocycle. The polarizability of aromatic systems is markedly anisotropic; the electron cloud is more polarizable in the plane of the ring and less so perpendicular to the plane of the ring. In comparison with the parent carbocycle, the main reduction in polarizability of the nitrogen heterocycle occurs in the direction normal to the molecular plane (198). Previous workers had concluded that the main reduction in polarizability in going from benzene to pyridine occurred along the dipolar axis (199).

3. Dipole moments

The significance of dipole data in determining charge distribution in pyridine has been pointed out. The experimental determination of pyridine's dipole moment has given values ranging from 2.2 D to 2.3 D. The dipole moment of pyridine vapor by microwave spectroscopy is 2.15 ± 0.05 D (65). Middleton and Partington (200) demonstrated that the solvent employed affects the value obtained from determinations run in solution. A carbon disulfide solution yields a value

of 2.10 D whereas carbon tetrachloride gives 2.33 D for the moment of pyridine.

Comparative dipole moment data for aza-aromatic heterocycles are given in Table 7 for determinations run in benzene (201, 202).

Table 7. Dipole moments of aza-aromatic heterocycles (benzene solution)

Heterocycle	μ (in Debye units)
pyridine	2.21
quinoline	2.14
isoquinoline	2.53
phenanthridine	1.50
acridine	1.95

4. Infrared spectra

Absorption of photons having a wave length between 2 and 15μ leads to vibrational excitations in a molecule. These may be stretching or deformation vibrations. Pyridines and quinolines exhibit the following stretching vibrational

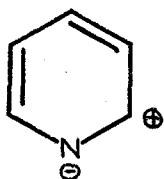
bands: CH near 3.3μ ; C=C and C=N in the region $6.0 - 6.3\mu$ and 6.5μ . Ring vibrations and CH deformation give bands in the regions, 8.4μ , $9-10\mu$ and $11-16\mu$. Although the ring vibrations of pyridine closely parallel those of benzene, hydrogen deformation vibrations are quite different and are shifted to lower frequencies. The C=C and C=N stretching bands are also slightly lower than those of benzene. In quinoline and isoquinoline the region between $6.3-6.7\mu$ has a more complex band structure (203).

5. Ultraviolet spectra

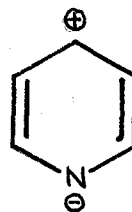
Electromagnetic radiation having a wave length between 2000 and 7500 \AA embraces the visible and ultraviolet region. Absorption of photons possessing energy of this range by a molecule may cause promotion of its electrons to higher electronic states. With conjugated molecules not only is the ground state energy lowered due to resonance but the energy levels of the excited states are sharply lowered. Because of this, the greater the length of a conjugated system the smaller will be the energy difference between the ground state and the lowest lying excited state. Thus naphthalene shows a bathochromic shift from the maximum in absorption of benzene, as less energetic (longer wave length)

photons are absorbed. As one passes through the series, benzene, naphthalene, anthracene, phenanthrene, naphthacene, pentacene and hexacene, this shift actually brings the absorption into the visible region and a colored molecule results.

From studies made by Mulliken (204) it can be concluded that the greater the increase of polarity of the molecule in the excited state, the greater is the intensity of absorption. As polar forms such as (LXIX and LXX) are more



LXIX



LXX

important in describing the excited states of pyridine, it is clear why pyridine has an ϵ_{max} of 2000 at 2500 Å while benzene has ϵ_{max} of 250 at 2600 Å. In addition, Maccoll (205) has pointed out that in the series, benzene, pyridine, pyrimidine, pyridazine and s-tetrazine, the maximum in absorption undergoes a bathochromic shift, the shift being most marked when hetero nitrogens are adjacent.

In examining the ultraviolet spectra of pyridine, quino-
line, isoquinoline, quinazoline, phenanthridine, 5,6-benzo-

quinoline and other heterocycles, Badger, Pearce and Pettit (206) drew these general conclusions. First, there is a considerable loss in fine structure in aza-aromatic heterocycles, but the maxima are not significantly shifted. The absorption shoulders of the nitrogen heterocycles begin, however, at slightly longer wave lengths. Second, the group III maxima between 2500-3500 \AA show a uniformly greater intensity in the nitrogen heterocycles.

6. Thermochemical data

The calculation of resonance energies from the observed heats of combustion of aromatic compounds and the use of bond energies is a well-known procedure (125). The values obtained for certain carbocycles and heterocycles are given in Table 8 (57). The values given show that the resonance energy of a given heterocycle is approximately the same as that of the parent carbocycle. From this it may be judged that isoquinoline and phenanthridine should have resonance energies of around 75 and 120 kilocalories per mole, respectively. The large resonance energies of pyridine, quinoline and acridine indicate that no single "static bond" structure can describe the heterocyclic molecule adequately.

Table 8. Empirical resonance energies of aromatic systems

Compound	Resonance Energy (kcal./mole)
benzene	41
naphthalene	77
anthracene	116
phenanthrene	130
pyrene	152
pyridine	43
quinoline	75
acridine	106
phenazine	105

G. Physiological Properties

Aza-aromatic heterocycles and their derivatives have received much attention from the biological chemist because of their pronounced physiological properties. The alkaloids studied by early natural product workers were found to contain such ring systems as the pyridine, quinoline and isoquinoline nuclei. Moreover, the dietary factors, nicotinic acid and pyridoxine, are now known to be pyridine derivatives.

With the advent of chemotherapy many research workers sought to modify the structures of known alkaloids, in order to obtain physiologically active agents which were less toxic. As a natural extension many basic derivatives of aza-aromatic heterocycles were screened for biological activity with considerable success. The vast amount of research carried out in this quest for chemotherapeutic agents is adequately covered in several reviews (207-210). Summarily, it might be stated that pyridine derivatives such as cetylpyridinium chloride and 5-amino-2-butoxypyridine are employed as antiseptics; isoquinoline systems are present in narcotics (heroin) and in antispasmodics (papaverine); quinoline and acridine derivatives (Atabrine, Plasmochin) are satisfactory anti-malarial agents; and phenanthridine compounds are effective trypanocidal agents against sleeping sickness in cattle and also in children.

In view of the diversified physiological activity of aza-aromatic heterocycles no comprehensive correlation of activity and chemical constitution is to be expected. Recently, however, Albert, Rubbs and Burvill (31) have made an extensive study of the antibacterial activity of aza-aromatic systems and proposed that the bacteriostatic action of these bases depends upon ionization and molecular shape. Acridines which were more than 50% ionized (as cations) at 37° were

found to exert a strong bacteriostatic action. Certain acridines possessed the required degree of cationic ionization but were only feebly antibacterial. These latter compounds all involved "dimensional factors". For example, 9-amino-1,2,3,4-tetrahydroacridine is shown by Hirschfelder models to be non-planar. Proceeding from Ehrlich's principle (210) "Corpora non agunt nisi fixata", the authors proposed that the acridine cations are attracted to the anions of nucleoproteins and lie flat on the bacterial surface. The stability of this union is enhanced by the van der Waals forces arising from the large aromatic π cloud. If the molecule has too small a planar area (pyridines and quinolines) or if it is less planar due to hydrogenation (9-amino-1,2,3,4-tetrahydroacridine), van der Waals forces cannot maintain the drug-protein union. Bulky side chains can inhibit this planar union also. As support for this hypothesis, inactive 2-methylquinolines could be changed into effective bacteriostats by condensing them with benzaldehyde. Presumably the planar styryl side chain enhanced the flat area of the molecule and thus increased the secondary forces of attraction. From related experiments the authors concluded that the critical area of the molecular plane should be between 28 and 38 \AA^2 .

III. EXPERIMENTAL

All reactions involving organometallic compounds were carried out in an apparatus which may be generalized thus. The setup consisted of a three-necked, round-bottomed flask equipped with a Trubore stirrer, graduated dropping funnel and a Friedrich condenser. The glassware, previously dried in an oven, was assembled while still warm. The reaction system was flushed with dry, oxygen-free nitrogen and kept under a positive pressure of nitrogen during the reaction.

All melting points were taken on an electrically heated copper block and are corrected. The infrared spectra referred to in this thesis were obtained on a Baird, model B, recording infrared spectrophotometer, property of the Institute for Atomic Research. Unless otherwise stated, spectral data for solid compounds were obtained from samples suspended in Nujol.

A. Preparation of Biphenyl Intermediates

1. 2-Acetaminobiphenyl

Scarborough and Waters (211) prepared this compound by the reaction of acetyl chloride with 2-aminobiphenyl in dry

pyridine. In this worker's hands the method gave a 64% yield of pure material. The following procedure, however, was more convenient and gave excellent results.

In a one-liter, three-necked flask equipped with a condenser, stirrer and addition funnel were placed 200 g. (1.17 moles) of 2-aminobiphenyl and 200 ml. of dry benzene. The contents were warmed to attain solution and then 120 g. (1.17 moles) of acetic anhydride were introduced in 55 minutes. The flask was intermittently cooled with an ice bath to control the reaction. A solid began to precipitate but the stirring was continued for 45 minutes. The chilled suspension was filtered to give 158.5 g. (63.1%) of white needles, m.p. 119.0-120.5°.

The filtrate was distilled to remove 115 ml. of solvent and the residue poured into one liter of water. The pink solid was collected, washed with water and dried. The light pink product weighed 70.2 g. and melted at 119.0-120.5°. The total yield was 229 g. (92.7%). The reported melting point of 2-acetaminobiphenyl is 121°.

2. 2-Acetamino-5-bromobiphenyl

This procedure is essentially that of Scarborough and Waters (211). In a one-liter, three-necked flask equipped

as above were placed 30.0 g. (0.142 mole) of 2-acetaminobiphenyl and 300 ml. of glacial acetic acid. To the cooled solution were added 22.9 g. (0.143 mole) of bromine in acetic acid over 90 minutes. After stirring for two hours the solution was allowed to stand overnight. The mixture was poured into two liters of water and sodium hydrogen sulfite added to discharge the bromine color. Filtration and drying gave 40.5 g. (98.5%) of white solid, m.p. 125-127°. Recrystallization from dilute ethanol gave 34.8 g. (84.5%) of colorless needles, m.p. 128.5-129.5°. The reported melting point is 130°.

3. 2-Acetamino-4'-chlorobiphenyl

A 250 ml., three-necked flask equipped in the usual manner was charged with 50.0 g. (0.245 mole) of 2-amino-4'-chlorobiphenyl and 100 ml. of dry benzene. After the mixture was warmed gently to attain solution, 26.5 g. (0.259 mole) of acetic anhydride were added dropwise over 20 minutes. The exothermic reaction was moderated by external cooling. The mixture was stirred for an additional hour and then 30 ml. of benzene were distilled off. Cooling of the remaining solution deposited 39.0 g. (64.6%) of colorless needles, m.p. 124-125°. The filtrate was distilled to remove

the benzene and the residue poured into water. The precipitated white solid upon filtration and drying gave 19.3 g. of product, m.p. 121-124°. Thus a 96.6% yield of 2-acetamino-4'-chlorobiphenyl was obtained. Since this compound has not been reported, an analytical sample melting at 124.5-125.0° was obtained from dilute ethanol.

Anal. Calcd. for $C_{14}H_{12}ClNO$: Cl, 14.43; N, 5.70.
Found: Cl, 14.31, 14.58; N, 5.67, 5.81.

4. 2-Amino-2'-nitrobiphenyl

The procedure followed was essentially that of Purdie (212) except that the crude amine was used directly for acetylation.

In a one-liter, three-necked flask equipped as usual were placed 29.0 g. (0.119 mole) of 2,2'-dinitrobiphenyl and 250 ml. of 95% ethanol. To the refluxing solution was added dropwise a solution of sodium polysulfide which was prepared by stirring 8.3 g. (0.259 g. atom) of sulfur into a warm solution of 33.2 g. (0.138 mole) of sodium sulfide nonahydrate in 100 ml. of water. After the 30 minute addition period the orange solution was refluxed for three hours and then allowed to stand overnight.

The mixture was distilled to remove 200 ml. of ethanol and the residue poured into one liter of water. The aqueous mixture was extracted with four 400 ml. portions of ether. These extracts were washed with water, dried over pellet potassium hydroxide and distilled to remove the solvent. The semi-solid residue was acetylated directly.

5. 2-Acetamino-2'-nitrobiphenyl

The above product was taken up in 75 ml. of dry benzene and placed in a 250 ml., three-necked flask as above. Acetic anhydride (11.0 ml.) was added dropwise in 20 minutes. An evolution of heat accompanied the formation of an orange suspension. After an additional hour the mixture was filtered to give 16.5 g. (54%) of cream-colored product, m.p. 158.5-159.5°. Purdie reports a melting point of 159°.

The filtrate was distilled to remove 70 ml. of benzene and the residue poured onto crushed ice. The pasty, light brown solid was recrystallized from benzene to give 8.4 g. (27%) of product melting at 157-159°.

6. 2-Acetamino-3-nitrobiphenyl

The procedure of Sako (213) was followed to obtain this compound in low yield.

2-Acetaminobiphenyl (42.2 g., 0.200 mole) was dissolved with heating in a mixture of 30 ml. of acetic anhydride and 30 ml. of glacial acetic acid contained in a 250 ml., three-necked flask equipped with a thermometer, stirrer and addition funnel. The contents were held at 22° by a water bath, while 20 g. of fuming nitric acid in 15 ml. of glacial acetic acid were added over a period of 100 minutes. The original mush of crystals gave way to a red solution, as the reaction mixture was stirred at 24° for three hours. After the flask had stood in the cold overnight, the contents were treated with 600 ml. of water. The suspension was extracted with two 250 ml. portions of benzene and these extracts were cooled. Twelve grams of solid were precipitated which melted from 168 to 180° (Sako obtained 9 g.). Recrystallization from benzene gave a pale yellow solid, m.p. 186.5-188.0°.

7. 2-Butyraminobiphenyl

A 500 ml., round-bottomed flask was equipped with a short air condenser which in turn bore a cork bearing a thermometer and bent glass tube. The latter tube led to an Erlenmeyer flask. The reaction flask was charged with 33.9 g. (0.200 mole) of practical grade 2-aminobiphenyl, 35.4 g. (0.400 mole) of n-butyric acid and 0.1 g. of zinc dust. The

flask was electrically heated for six hours, during which time an azeotropic mixture of n-butyric acid and water distilled into the trap together with some excess acid. The warm reaction mixture was poured into 300 g. of ice and stirred until it solidified. Upon filtration 46.4 g. of pink solid smelling strongly of n-butyric acid were obtained which melted over the range 50-58°. Recrystallized from dilute ethanol the white product weighed 38.2 g. (80%) and melted at 83-85°. The analytical sample was obtained as long, white needles from petroleum ether (b.p. 60-70°), m.p. 86.0-86.5°.

Anal. Calcd. for $C_{16}H_{17}NO$: N, 5.87. Found: N, 5.74, 5.85.

8. 2-Valeraminobiphenyl

In the same apparatus employed for the preparation of 2-butyraminobiphenyl were placed 33.9 g. (0.200 mole) of 2-aminobiphenyl, 40.9 g. (0.400 mole) of n-valeric acid and 0.1 g. of zinc dust. This was heated at incipient reflux for eight hours and then poured into ice. The solid was filtered off, washed with large amounts of water and dried. The pale pink solid weighed 55.1 g. and melted over the range 63-67°. Recrystallized from dilute ethanol the white solid weighed

41.8 g. (82%), m.p. 68-70°. Long, white needles, m.p. 73.0-74.5°, were obtained from petroleum ether (b.p. 60-70°).

Anal. Calcd. for $C_{17}H_{19}NO$: N, 5.53. Found: N, 5.45, 5.36.

9. N,N'-Di(α -xenyl) oxalamide

In the course of preparing 2-carbethoxyaminobiphenyl by heating equimolar quantities of 2-aminobiphenyl and diethyl oxalate, Walls (15) isolated a small amount of by-product whose analysis fitted the diamide. A convenient preparation is as follows.

Diethyl oxalate (29.2 g., 0.20 mole) and 2-aminobiphenyl (67.6 g., 0.40 mole) were heated between 135 and 175° for seven hours. Ethanol (13 ml.) readily distilled out of the reaction mixture. The temperature was raised to 185° for two hours. After a final one hour heating at 110° under vacuum, the mixture was refluxed with 100 ml. of methanol and filtered hot. The residue consisted of 28.6 g. (36.5%) of almost colorless needles, m.p. 220-225°. Recrystallized from benzene 25.2 g. of white needles were obtained, m.p. 238.0-238.5°. The reported melting point is 233-235°.

B. Phenanthridine Derivatives by Cyclization

1. 6-n-Propylphenanthridine

A 500 ml. flask was charged with 23.9 g. (0.100 mole) of 2-butyraminobiphenyl and 38.0 g. (0.248 mole) of phosphorus oxychloride. An air condenser bearing a calcium chloride tube was then attached to the flask. The latter tube in turn was connected to a rubber tube leading to a funnel inverted over sodium hydroxide solution. The reaction mixture was heated moderately until hydrogen chloride began to evolve. Heat was withdrawn and the vigorous reaction proceeded spontaneously for 15 minutes. Heat was re-applied and the mixture refluxed for two hours, at the end of which time gas evolution had ceased. The excess phosphorus oxychloride was removed under reduced pressure. The residue was extracted with six 50 ml. portions of hot 6 N hydrochloric acid. These extracts were filtered through glass wool and then made basic with sodium hydroxide. The oil liberated was taken up in 200 ml. of ether and benzene. After drying, the solvent was removed and the residue distilled under reduced pressure. The main fraction was 16.0 g. (73%) of a pale yellow liquid (b.p. 164-166° at 2.0 mm.), n_D^{20} 1.6552.

Anal. Calcd. for $C_{16}H_{15}N$: N, 6.33. Found: N, 6.69.

The picrate formed fine, bright yellow needles from a dioxane-ethanol pair, m.p. 196.0-197.5°.

Anal. Calcd. for $C_{22}H_{18}N_4O_7$: N, 12.44. Found: N, 12.20, 12.25.

2. 6-n-Butylphenanthridine

The apparatus described above for the preparation of 6-n-propylphenanthridine was employed unchanged. The 2-valeraminobiphenyl (25.5 g., 0.100 mole) and phosphorus oxychloride (41.8 g., 0.270 mole) were heated until the reaction began. After the spontaneous reaction had subsided, the red solution was refluxed for two hours. The excess phosphorus oxychloride was then distilled off under reduced pressure. The residue was extracted with four 50 ml. portions of 6 N hydrochloric acid and the extracts filtered through glass wool. The base was freed with sodium hydroxide and taken up in a mixture of ether and benzene. The dried solution was distilled to remove the solvent and the residue subjected to vacuum distillation. The main fraction was 14.0 g. (60%) of a pale orange, viscous liquid, b.p. 182-184° at 4.0 mm. The analyses of this compound and its picrate are given in Section C.

3. 2-Bromo-6-methylphenanthridine

In the same setup used for the preparation of 6-n-propylphenanthridine 30.0 g. (0.103 mole) of 2-acetamino-5-bromobiphenyl were refluxed in 42 g. (0.275 mole) of phosphorus oxychloride for two hours. The excess phosphorus oxychloride was distilled off and the residue extracted with six 50 ml. portions of hot 6 N hydrochloric acid. Treatment of these extracts with concentrated ammonium hydroxide gave upon filtration 23.5 g. (84%) of tan solid melting over the range 125-128°. From dilute ethanol 20.2 g. (72%) of colorless needles were obtained, m.p. 127.5-128.5°. Barber and co-workers (214) report this compound to melt at 128°.

4. 6-Methyl-4-nitrophenanthridine

This compound was prepared analogous to the procedure of Stepan and Hamilton (215). Two grams of 2-acetamino-3-nitrobiphenyl were refluxed with 10 ml. of phosphorus oxychloride for one hour. After hydrolysis and collection of the solid, the product was recrystallized from ethanol to yield white needles, m.p. 165-166°. The reported melting point is 167°.

5. 6-Methyl-10-nitrophenanthridine

2-Acetamino-2'-nitrobiphenyl (2.0 g., 0.0078 mole) and phosphorus oxychloride (10 ml.) were gently refluxed for one hour. The contents were cautiously hydrolyzed and then extracted with two 50 ml. portions of hot 6 N hydrochloric acid. The yellow extracts were made basic with ammonium hydroxide and the base was collected on a filter. It weighed 1.3 g. (69%) and melted over the range 170-190°. Recrystallization from ethanol (Norit) gave silky, pale yellow needles, m.p. 192.0-193.0°.

Anal. Calcd. for $C_{14}H_{10}N_2O_2$: N, 11.76. Found: N, 11.64, 11.48.

6. 6,6'-Diphenanthridyl (attempted)

a. Phosphorus oxychloride and nitrobenzene. N,N'-Di(o-xenyl) oxalamide (9.8 g., 0.025 mole) was refluxed with 30 ml. of phosphorus oxychloride and 30 ml. of nitrobenzene for six hours. Although the solution darkened, no hydrogen chloride was evolved. The phosphorus oxychloride was then distilled off and the residue treated with cold water. Collection of the crystals and washing with ether gave 9.4 g. of white needles, m.p. 237.0-238.5°. A mixed melting point

determination confirmed that the original amide was recovered in 98% yield.

b. Polyphosphoric acid. A mixture of 9.8 g. (0.025 mole) of N,N'-di (p-xenyl) oxalamide and 50 g. of polyphosphoric acid (Victor Chemical) was stirred at 200° for 18 hours. The original gray paste was dark green at the end of this time. The cooled mixture was hydrolyzed with ice water and then made basic with ammonium hydroxide. The gray precipitate upon collection and drying weighed 9.4 g. and melted over the range 225-234°. Again, purification showed this solid to be starting material.

C. Chemistry of the Phenanthridine System

1. Alkylation and arylation

a. 6-n-Butylphenanthridine. In attempting the metalation of phenanthridine by n-butyllithium, it was realized that a very low temperature would be necessary to avoid addition to the azomethine linkage.

Twenty grams (0.112 mole) of phenanthridine were suspended in 200 ml. of dry ether in a 500-ml., three-necked flask fitted in the usual manner except a low-temperature thermometer was substituted for the condenser. The contents

were cooled to -45° by an alcohol-Dry Ice bath. Then 0.111 mole of freshly prepared n-butyllithium (216) in 120 ml. of ether was added in 20 minutes. The temperature was lowered to -50° and held there for 15 minutes. The suspension became chartreuse and finally formed a fluorescent green solution during this time. The reaction mixture was rapidly poured onto a slurry of Dry Ice in anhydrous ether. After the Dry Ice had disappeared, the residue was extracted with 200 ml. of 5% potassium hydroxide solution. Separation and acidification of the aqueous layer gave no precipitate.

The ethereal layer of the hydrolyzed carbonated mixture was dried over sodium sulfate and distilled to remove the solvent. The orange residue was refluxed with 30 ml. of nitrobenzene for 20 minutes to oxidize the dihydro form. The nitrobenzene was removed at the water pump and the residue distilled at the oil pump. The main fraction was 23.7 g. (90%) of 6-n-butylphenanthridine, b.p. $177-178^{\circ}$ at 3.4 mm., n_D^{20} 1.6369. The infrared spectrum indicated that some dihydro form was still present in the product. There was an NH band at 3.0μ , together with bands at 3.3, 3.45 and 3.55μ (CH), 6.22 and 6.35μ (C=C and C=N) and 13.2 and 13.8μ (o-disubstituted benzene).

The analytical sample was obtained as a pale yellow liquid, b.p. 184° at 4.0 mm. by redistilling through a short fractionation column.

Anal. Calcd. for $C_{17}H_{17}N$: N, 5.96. Found: N, 6.06.

A picrate was prepared as fine, yellow needles and recrystallized from a dioxane-ethanol pair, m.p. 195.5-197.0°.

Anal. Calcd. for $C_{23}H_{20}N_4O_7$: N, 12.06. Found: N, 12.21, 12.01.

It is interesting to note that when the reaction between phenanthridine and n-butyllithium was conducted at room temperature and coupled with an 11 hour reflux period, the yield was 88%.

b. 6-n-Propylphenanthridine. In a 500 ml., three-necked flask equipped in the usual fashion were placed 21.1 g. (0.117 mole) of phenanthridine and 150 ml. of dry ether. To the stirred suspension was added 0.247 mole of n-propylmagnesium bromide in 120 ml. of ether. The resulting yellow suspension was stirred under reflux for 100 hours, during which time most of the solid dissolved to form a dark solution. The cooled reaction mixture was hydrolyzed with ammonium chloride solution and the organic layer was separated. After drying the extract over anhydrous sodium sulfate, the solvent was removed and the residual oil was refluxed with 30 ml. of nitrobenzene for 30 minutes. The nitrobenzene was distilled off at the water pump and the orange oil remaining was fractionated under reduced pressure. The main fraction consisted of 18.4 g. of yellow liquid, b.p. 163-164° at 1.9

mm., n_D^{20} 1.6525. Redistillation of the forerun gave an additional 3.4 g. of product for a total crude yield of 84%. A picrate was prepared and crystallized from dioxane as yellow needles, m.p. 193.5-195°. Admixed with authentic 6-n-propylphenanthridine picrate (m.p. 196.0-197.5°), the picrate melted at 194-197°. The infrared spectra of these picrates were almost superimposable.

c. 6-o-Tolyl-5,6-dihydrophenanthridine. o-Tollyllithium was prepared analogous to phenyllithium from 3.5 g. (0.50 g. atom) of lithium wire and 39.3 g. (0.230 mole) of o-bromotoluene in 88% yield.

In a one-liter, three-necked flask set up in the usual manner were placed 30.0 g. (0.168 mole) of phenanthridine and 200 ml. of dry ether. Then 0.196 mole of o-tollyllithium in 180 ml. of ether was added over 50 minutes. The reactants were stirred for three hours at room temperature after which time a fluorescent green solution had been obtained. After stirring for an additional four hours the reaction mixture was hydrolyzed, and the suspended solid was filtered off. This cream-colored solid weighed 9.3 g. and melted over the range, 134-138°. After removal of the solvent the ether layer yielded additional product (26.7 g.) of the same melting range. The total crude yield was 36.0 g. (74%). One recrystallization from an ethanol-benzene pair gave

31.5 g. (64%) of slightly tan crystals, m.p. 140-141°. Although the infrared spectrum had no sharp NH band, the compound gave an orange precipitate with picric acid. The analytical sample melted at 140.5-141.5°.

Anal. Calcd. for $C_{20}H_{17}N$: N, 5.16. Found: N, 5.15, 5.12.

d. Dehydrogenation of 6-o-tolyl-5,6-dihydrophenanthridine. The apparatus used for the dehydrogenation was an 8 mm. test tube fitted through a ground glass joint to a cold finger condenser which extended down to 3 mm. from the bottom. The test tube was fitted with a gas-inlet and -outlet in order that nitrogen might be passed through the tube to sweep out any hydrogen. The apparatus served excellently for small-scale preparations.

In the tube were placed 1.00 g. of 6-o-tolyl-5,6-dihydrophenanthridine, 100 mg. of 5% palladium on Darco and 5 ml. of mesitylene. The reaction mixture was refluxed for one hour while a rapid stream of nitrogen was passed through the tube. At the end of this time the initial blue fluorescence of the solution had disappeared. The mixture was filtered and the catalyst was washed with 10 ml. of ether. The ether and mesitylene were distilled off, leaving an oily yellow residue. Since only oils were obtained from 95% ethanol, the base was converted to the picrate. A crystalline

yellow solid melting at 165-167° and weighing 1.6 g. (87%) was obtained. 6-p-Tolylphenanthridine picrate formed bright yellow prisms from 95% ethanol, m.p. 167.5-168.0°.

Anal. Calcd. for $C_{26}H_{18}N_4O_7$: N, 11.24. Found: N, 11.41.

e. 6-Benzyl-5,6-dihydrophenanthridine. Benzylmagnesium chloride was prepared in 90% yield by the interaction of 7.3 g. (0.30 g. atom) of magnesium turnings and 39.4 g. (0.31 mole) of benzyl chloride in ether.

In a 500 ml., three-necked flask equipped as usual were placed 32.3 g. (0.180 mole) of phenanthridine and 100 ml. of dry ether. Over 30 minutes 0.26 mole of benzylmagnesium chloride in 190 ml. of ether was added. The initially formed bright yellow slurry slowly changed to a dark green solution when the reaction mixture was refluxed for 24 hours. The solution was hydrolyzed with saturated ammonium chloride solution and the resulting suspended solid was filtered off. This white solid weighed 38.2 g. (78%) and melted over the range 128-133°. Recrystallizations from an ethanol-benzene pair gave well-formed, glistening white prisms but the melting range could not be narrowed. The infrared spectrum showed bands at 3.05 μ (NH), 6.23 μ (C=C), 13.3 and 13.8 μ (p-disubstituted benzene) and 14.3 μ . The product was submitted for analysis.

Anal. Calcd. for $C_{20}H_{17}N$: C, 88.52; H, 6.32; N, 5.17.
Found: C, 87.90; H, 6.66; N, 5.41.

The product could not be dehydrogenated by heating with nitrobenzene. A solid of the same melting range was recovered from such an attempted dehydrogenation.

f. 6-Benzoylphenanthridine. To characterize the impure product resulting from the interaction of phenanthridine and benzylmagnesium chloride, it was oxidized to the known 6-benzoylphenanthridine.

The impure 6-benzyl-5,6-dihydrophenanthridine (6.8 g., 0.025 mole) dissolved in 100 ml. of warm glacial acetic acid was treated with 14.3 g. (0.047 mole) of sodium dichromate in the course of 20 minutes. The green solution which resulted was refluxed for 90 minutes and then poured into water. Cooling and filtration gave 7.0 g. (99%) of pale yellow solid, melting over the range $140-147^{\circ}$. From ethanol 5.1 g. (72%) of white solid melting at $150-152^{\circ}$ were obtained. Another recrystallization gave white plates, m.p. $152-154^{\circ}$. The product gave a positive test for the carbonyl group with a solution of 2,4-dinitrophenylhydrazine and the infrared spectrum exhibited a band at 6.0μ . Ritchie (21) reports that 6-benzoylphenanthridine melts at 152° .

g. Bis-6-phenylphenanthridine. When Gilman and Nelson (217) treated 6-phenylphenanthridine with *p*-tolyllithium or

with mesityllithium, a pale yellow solid melting at 275-277° was obtained in each case. This solid was thought to be a bis-6-phenylphenanthridine, but no structure was proposed. The compound contained 5.48% nitrogen and gave a molecular weight of 522.

This compound was reconsidered in this study. It was felt that the yellow product might have resulted from the reductive coupling of 2 molecules of 6-phenylphenanthridine.

Anal. Calcd. for $C_{38}H_{28}N_2$: C, 89.03; H, 5.55; N, 5.47; mol. wt., 513. Found: C, 89.02, 88.97; H, 5.66, 5.79.

The infrared spectrum showed bands at 2.98 and 3.08 μ (NH), 6.3 μ (C=C) and 13.2, 13.8 and 14.3 μ (substituted benzene).

2. Bromination

a. N-Bromosuccinimide method. In a 500 ml., three-necked flask fitted with a stirrer and condenser were placed 17.9 g. (0.100 mole) of phenanthridine, 17.8 g. (0.100 mole) of N-bromosuccinimide and 125 ml. of carbon tetrachloride. The flask was wrapped in aluminum foil to exclude any photocatalysis. The reaction mixture was stirred under reflux for 48 hours during which time the solvent became orange in color and the walls of the flask were coated with a reddish-orange

gum. Carbon tetrachloride (50 ml.) was added and the hot solution was filtered. The filtered solution was concentrated to 30 ml. and 14.1 g. (55%) of cream-colored solid were deposited, melting over the range 135-145°. From 150 ml. of 95% ethanol the solid came down as colorless needles, 9.0 g., m.p. 156-159°. Another recrystallization from the same solvent gave 7.9 g. (31%), m.p. 160-162.5°. The analytical sample melted at 162-163°. The compound was unchanged by boiling sodium hydroxide solution, but was soluble in warm, dilute hydrochloric acid. An elemental qualitative analysis confirmed the presence of bromine.

Anal. Calcd. for $C_{13}H_8BrN$: Br, 30.96; N, 5.43. Found: Br, 30.98, 30.96; N, 5.50, 5.29.

The picrate was obtained from dioxane as yellow needles, m.p. 251.0-252.5°.

Anal. Calcd. for $C_{19}H_{11}BrN_4O_7$: N, 11.50. Found: N, 11.44, 11.56.

The infrared spectrum was similar to that of phenanthridine itself; however, the bromophenanthridine exhibited a sharp band at 12.18μ . Since this latter band is characteristic of *p*-disubstituted benzene rings, the bromine seemed to occupy the 3-, 8-, 9- or, most likely, the 2-position. That the bromine was at the 2-position was demonstrated by oxidation to the known 2-bromophenanthridone (Part e).

b. Phenanthridine hydrobromide perbromide method. Phenanthridine (27.0 g., 0.150 mole) and 75 ml. of 48% hydrobromic acid were thoroughly mixed and the excess acid was distilled off under reduced pressure. The dry yellow solid was mixed with 200 ml. of glacial acetic acid and 15 ml. of bromine were added. The reddish-orange mixture was heated for 30 minutes with frequent shaking. Upon cooling the solid was filtered off and washed with acetic acid. The orange needles weighed 61.7 g. (97%) and melted at 180.0-181.5°.

The phenanthridine hydrobromide perbromide was heated in a 500 ml. flask for six hours at 200°. At first bromine was evolved and then hydrogen bromide came off slowly. The cooled reaction mass was heated with 100 ml. of 15% potassium hydroxide solution, and the liberated base was taken up in 250 ml. of ether and benzene. The extracts were dried over anhydrous sodium sulfate and the solvent was removed. The residue was distilled under reduced pressure into the following fractions: (1) 8.1 g., 165-172° at 4.0 mm., m.p. 85-99°; (2) 7.0 g., 172-176° at 4.5 mm., m.p. 80-93°; (3) 2.0 g., 176-185° at 4.5 mm., m.p. 75-110°; (4) 3.7 g., 185-192° at 2.9 mm., m.p. 85-125°; (5) 2.1 g., 193-200° at 3.5 mm., m.p. 85-130°; and (6) 3.2 g., 200-215° at 3.6 mm., m.p. 115-130°. Fractions (1) and (2) were mainly recovered phenanthridine; fractions (3) and (4) upon recrystallization from 95%

ethanol gave white needles, m.p. 159-161°. This product proved to be identical with the bromophenanthridine obtained in Part a by mixed melting points of the bases and their picrates. Fractions (5) and (6) upon repeated recrystallization from 95% ethanol gave cream-colored needles melting over the range 218-227°, which were not further purified.

For the bromination of phenanthridine this method was inferior to the N-bromosuccinimide method. It seemed that more by-products were formed due to the stringent conditions.

c. Bromine-glacial acetic acid method. Phenanthridine (17.9 g., 0.100 mole) and bromine (16.0 g., 0.100 mole) were refluxed in 100 ml. of glacial acetic acid for 24 hours. The flask was covered with aluminum foil to prevent any photocatalysis. In the course of the reaction the initially formed orange suspension changed to a clear, dark red solution, and hydrogen bromide was evolved. After the reaction solution had cooled, it was poured into water and treated with ammonium hydroxide. The liberated base upon filtration and drying weighed 19.6 g. and melted over the range 87-95°. This product was dissolved in 200 ml. of ethanol (Norit) and filtered. The cooled solution deposited 5.4 g. (21%) of cream-colored solid which melted from 148 to 153°. Two additional recrystallizations yielded white needles, m.p. 160.0-161.5°. Admixed with the bromophenanthridine obtained

in Section III, C, 2, a it melted undepressed. The picrates of these two bromophenanthridines also did not depress each other's melting point when admixed.

d. Bromine-carbon tetrachloride method (attempted).

In a 250 ml., three-necked flask fitted with a condenser and stirrer were placed 17.9 g. (0.100 mole) of phenanthridine, 16.0 g. (0.100 mole) of bromine and 200 ml. of carbon tetrachloride. An orange suspension formed with the evolution of heat. This orange suspension underwent no visible change after stirring 24 hours under reflux. The orange solid was filtered off and then suspended in water. After treatment with sodium hydroxide and sodium sulfite the orange suspension became cream-colored. Collection of the solid gave 15.0 g. melting at 105-107°. A mixed melting point determination showed the solid to be starting material.

The original carbon tetrachloride filtrate gave upon concentration 1.0 g. of orange solid, m.p. 153-155°. This seemed to be a perbromide of phenanthridine, as 0.6 g. of phenanthridine was isolated by treatment with base. The total recovery of phenanthridine was 15.6 g. (87%) and no bromophenanthridine was obtained.

e. Oxidation of the unknown bromophenanthridine. The unknown bromophenanthridine obtained above (2.0 g.), 55 ml. of water and 5 ml. of concentrated sulfuric acid were warmed

to attain solution. To the warm solution were added 3.2 g. of solid potassium permanganate over 30 minutes (22). Effervescence and the odor of free halogen were observed during the reaction. After two hours the brown suspension was filtered. The brown solid was extracted with two 40 ml. portions of boiling pyridine. The pyridine extracts were concentrated and cooled to yield 0.83 g. (39%) of cream-colored solid, melting over the range 322-326°. One recrystallization from nitrobenzene gave fluffy white needles, m.p. 325.5-326.5°. Admixed with authentic 2-bromophenanthridone it melted at 325.5-327.0°. Comparison of infrared spectra also confirmed that it was identical with 2-bromophenanthridone. Thus, the starting monobromophenanthridine must have been the 2-bromo isomer.

The odor of free bromine was shown to stem from secondary degradation reactions thus. When an authentic sample of 2-bromophenanthridone was warmed with aqueous potassium permanganate and sulfuric acid, bromine vapor was immediately evolved and detected with starch-iodide paper.

f. 2-Cyanophenanthridine. In a 100 ml., round-bottomed flask were placed 2.5 g. (0.0097 mole) of 2-bromophenanthridine, 2.5 g. (0.031 mole) of copper (I) cyanide and 20 ml. of pure, dry quinoline. The tan suspension was heated in an oil bath at 190° for 24 hours. The cooled mixture was

extracted with two 40 ml. portions of hot ethanol. These filtered extracts deposited 2.5 g. of pale green needles. As this solid was partially inorganic, it was re-extracted with ethanol. From the latter extract was obtained 1.0 g. (50%) of white needles, m.p. 216.0-217.5°. The analytical sample melted at 216.5-217.5°.

Anal. Calcd. for $C_{14}H_8N_2$: N, 13.72. Found: N, 13.65, 13.78.

The infrared spectrum exhibited characteristic bands at 4.5 μ ($C\equiv N$) and 11.9 μ (p-disubstituted benzene).

3. Cyanation

a. Phenanthridine methiodide. In a one-liter flask were placed 26.7 g. (0.149 mole) of phenanthridine, 24 ml. of methyl iodide and 200 ml. of dry benzene. The orange solution was refluxed for four hours during which time a yellow solid was deposited. This yellow powder was collected and the filtrate refluxed for two more hours to yield additional product. The combined yellow solid was washed thoroughly with ether and dried. In this manner 44.8 g. (93.7%) of the methiodide were obtained, m.p. 203-204°. Pictet and Ankersmit (5) report a melting point of 202°.

b. 6-Cyano-5-methyl-5,6-dihydrophenanthridine. Phenanthridine methiodide (32.1 g., 0.100 mole) was suspended in 350 ml. of 95% ethanol and treated with 10.0 g. (0.154 mole) of potassium cyanide in 75 ml. of water. The pale yellow solid quickly disappeared and a white solid was formed. The mixture was warmed to attain solution and set aside to cool. The precipitated white needles were collected and dried, 17.9 g. (81%), m.p. 117-118°. Dilution of the filtrate with water yielded an additional 3.2 g. for a total yield of 96%. Tinker (218) reports a melting point of 120°.

c. 6-Cyanophenanthridine methiodide. 6-Cyano-5-methyl-5,6-dihydrophenanthridine (11.0 g., 0.050 mole) was dissolved in 150 ml. of pure pyridine. The resulting solution was poured with stirring into a solution of 12.7 g. (0.050 mole) of iodine in 200 ml. of ethanol. Immediately the iodine color was discharged and a brown precipitate appeared. An additional 150 ml. of ethanol was added to the suspension to complete the precipitation of the product. Filtration gave 15.6 g. (90%) of shiny, light brown platelets, m.p. 163.0-163.5°. Recrystallization from an ethanol-pyridine pair did not change the melting point.

4. Friedel-Crafts reaction (attempted)

To 100 ml. of nitrobenzene in a one liter flask were added 10.0 g. (0.056 mole) of phenanthridine and 24.0 g. (0.182 mole) of anhydrous aluminum chloride. Finally, 13.5 g. (0.091 mole) of phthalic anhydride were introduced and the flask stoppered with a calcium chloride tube. With periodic shaking the mixture was allowed to stand at room temperature for seven days. The reactants formed a dark green solution with a small amount of suspended solid. At the end of this time the mixture was poured into a slurry of ice and concentrated hydrochloric acid. The suspension was extracted with five 100 ml. portions of ether. The aqueous layer was made strongly alkaline and the liberated cream-colored solid filtered off. This weighed 9.5 g. (95% recovery) and melted at 103-105°. A mixed melting point showed it to be phenanthridine.

5. Hydroxylation

The Chichibabin hydroxylation reaction (27) was found to be applicable to phenanthridine. Two preliminary attempts employing pellet potassium hydroxide were unsuccessful, however, due to the fact that the reagent contained about 10%

water. Preliminary fusion of the potassium hydroxide and inclusion of barium oxide provided a satisfactory hydroxylating agent.

In a 250 ml., round-bottomed copper flask were placed 10.0 g. (0.056 mole) of phenanthridine, 20.5 g. of fused and crushed potassium hydroxide and 5.0 g. of barium oxide. The flask was connected through a safety flask to a rubber tube immersed in water. This served to observe the rate of hydrogen evolution. The flask was heated in a metal bath at $225 \pm 5^\circ$. After 30 minutes the vigorous gas evolution had virtually ceased. After the reaction flask had been heated for an additional 30 minutes, the cooled mixture was eluted with three 60 ml. portions of dilute hydrochloric acid. The suspension was made basic with sodium hydroxide and then filtered. The tan solid weighed 12.2 g. It was recrystallized from 200 ml. of glacial acetic acid to give 7.3 g. (67%) of white solid, m.p. $290-292^\circ$. A sample of white needles was obtained from acetic acid, m.p. $292.5-293.5^\circ$. Admixed with authentic phenanthridone it melted undepressed.

6. 2-Nitrophenanthridine

The nitration of phenanthridine has been accomplished by dissolving phenanthridine nitrate in concentrated sulfuric

acid (13). Such conditions lead to a complex mixture of six mononitrophenanthridines from which Caldwell and Walls (22) isolated a 3% yield of crude 2-nitrophenanthridine.

In order to obtain 2-nitrophenanthridine for further studies, it was found advantageous to modify the procedure of Morgan and Walls (13). A mixture of acetic anhydride and acetic acid was substituted for the sulfuric acid in hopes of increasing the amount of 2-nitrophenanthridine formed.

A 500 ml., three-necked flask equipped with a stirrer and condenser was charged with 24.2 g. (0.15 mole) of phenanthridine nitrate, 75 ml. of acetic anhydride and 75 ml. of glacial acetic acid. The white slurry was heated up to 60° in an oil bath and held there for one hour. During this time a pale yellow solution formed. After standing overnight the mixture was heated at 80° for an additional hour, and the red solution was then poured into water. The base was liberated with ammonium hydroxide, collected and dried. A quantitative yield (22.4 g.) of nitrophenanthridines was obtained, melting over the range 86-200°. Extraction of this solid with 200 ml. of ethanol left 3.8 g. of cream-colored solid, melting from 220° to 240° (17%). This crude 2-nitrophenanthridine, after two recrystallizations from glacial acetic acid, yielded 2.0 g. (9%) of pale yellow needles, m.p. 259-261°. 2-Nitrophenanthridine is reported to melt at 260-262° from glacial

acetic acid (13), and at 266-267° from an ethanol-ethoxy-ethanol pair (22).

7. Oxidation

a. Oxidation of phenanthridine (attempted). Phenanthridine (6.6 g., 0.033 mole) was heated with 14.3 g. (0.047 mole) of sodium dichromate in 100 ml. of glacial acetic acid for 24 hours. The initially red solution darkened somewhat during this time. The cooled solution was poured into water and the precipitated orange solid was collected and dried. Probably this was the dichromate salt of phenanthridine, for treatment with sodium hydroxide solution gave 7.0 g. of white solid, melting over the range 106-111°. When heated with 50 ml. of dilute hydrochloric acid and filtered, this solid dissolved almost completely leaving only a 0.1 g. residue. This residue melted around 280°, dec., but no phenanthridone could be isolated upon attempted recrystallization from glacial acetic acid.

b. Oxidation of 6-n-butylphenanthridine. In a 250 ml., three-necked flask fitted with condenser, stirrer and solids funnel were placed 7.8 g. (0.033 mole) of 6-n-butylphenanthridine and 100 ml. of glacial acetic acid. While the solution was held at incipient reflux, 14.3 g. (0.047 mole)

of sodium dichromate were added over 75 minutes. The initially orange solution turned dark green during two hours of reflux. The solution was poured into water and the precipitated tan solid was filtered off. The solid was extracted with two 100 ml. portions of ether. The residue weighed 2.3 g. (36%) and melted at 289-292°. A mixed melting point determination with an authentic specimen showed this to be phenanthridone.

Removal of solvent from the ether extracts left 4.0 g. (49%) of a dark yellow solid melting over the range 85-95°. Recrystallizations from 95% ethanol (Norit) gave silky, white needles, m.p. 108-109°. This solid proved to be 6-butyryl-phenanthridine. Its infrared spectrum showed an intense carbonyl band at 5.95 μ . Moreover, it formed derivatives with 2,4-dinitrophenylhydrazine and with picric acid.

Anal. Calcd. for $C_{17}H_{15}NO$: N, 5.62. Found: N, 5.50, 5.54.

The 2,4-dinitrophenylhydrazone was prepared in the usual manner. Successive recrystallizations from an ethanol-ethyl acetate pair and then a chloroform-ethanol pair gave light orange, matted needles, m.p. 158.5-161.0°.

Anal. Calcd. for $C_{23}H_{19}N_5O_4$: C, 64.32; H, 4.46. Found: C, 64.26, 64.35; H, 4.59, 4.63.

The picrate crystallized from a dioxane-95% ethanol pair as stout, yellow needles, m.p. 198-199°, dec.

Anal. Calcd. for $C_{23}H_{18}N_4O_8$: N, 11.71. Found: N, 11.65, 11.59.

c. Oxidation of 6-n-propylphenanthridine. In the same apparatus as used for 6-n-butylphenanthridine were placed 7.3 g. (0.033 mole) of 6-n-propylphenanthridine and 100 ml. of glacial acetic acid. After the solution was heated to incipient reflux, 14.3 g. (0.047 mole) of sodium dichromate were introduced over 40 minutes. After a three-hour reflux period, the mixture was poured into water and filtered to give 6.0 g. of pale yellow solid, melting over the range 245-265°. Extraction with two 50 ml. portions of ether left 3.4 g. (53%) of phenanthridone, m.p. 292-293°, as identified by a mixed melting point with an authentic specimen.

Removal of the ether from the extracts left 2.3 g. (30%) of yellow solid melting over the range 53-57°. Recrystallizations from 95% ethanol (Norit) gave white needles, m.p. 73-74°. That this compound was 6-propionylphenanthridine was supported by the infrared spectrum which showed a sharp band at 5.9μ . Moreover, it gave derivatives with 2,4-dinitrophenylhydrazine and with picric acid.

The 2,4-dinitrophenylhydrazone was repeatedly recrystallized from a chloroform-95% ethanol pair as orange prisms, m.p. 225.5-227.5°.

Anal. Calcd. for $C_{22}H_{17}N_5O_4$: C, 63.85; H, 4.12.

Found: C, 63.61; H, 4.26.

The picrate was obtained as chartreuse needles from a dioxane-95% ethanol pair, m.p. 195.5-197.0°.

Anal. Calcd. for $C_{22}H_{16}N_4O_8$: N, 12.08. Found: N, 12.34.

d. 4-Nitrophenanthridone. This compound was prepared by the dichromate oxidation of 6-methyl-4-nitrophenanthridine according to the directions of Stepan and Hamilton (215). They report a melting point of 257-258° (uncorr.). The product was obtained as bright yellow needles from acetic acid, m.p. 263-265° (corr.).

e. 10-Nitrophenanthridone. 6-Methyl-10-nitrophenanthridine (0.20 g.) and 10 ml. of glacial acetic acid were refluxed while 0.40 g. of sodium dichromate was added portionwise. The dark red color of the mixture turned dark green over the 30 minute reflux period. The mixture was poured into 100 ml. of water and the solid was collected (0.15 g.). After two recrystallizations from nitrobenzene light yellow needles were obtained, m.p. 322-323° with darkening. Caldwell and Walls (22) prepared this compound by the permanganate oxidation of 10-nitrophenanthridine in acid solution and report a melting point of 316-318°.

The infrared spectrum displayed bands at 3.2μ (NH) and 6.05μ (C=O).

f. 2-Bromophenanthridone. Walls (16) originally reported that dichromate oxidation of 2-bromo-6-methylphenanthridine gave a bright yellow solid melting at 302° with sintering which he considered to be 2-bromophenanthridone. Both Mosby (186) and this worker have reinvestigated the preparation of 2-bromophenanthridone. Mosby prepared this compound unambiguously by the Friedel-Crafts cyclization of 5-bromo-2-biphenyl isocyanate. He found the compound was actually a white solid melting at $323-324^{\circ}$. The writer, on the other hand, reached the same conclusion by reinvestigating Walls' reaction product.

In a 500 ml., three-necked flask equipped with a condenser, stirrer and solids funnel 28.5 g. (0.105 mole) of 2-bromo-6-methylphenanthridine were dissolved in 300 ml. of glacial acetic acid. While the solution was heated to incipient reflux, 45.0 g. (0.151 mole) of powdered sodium dichromate were added in the course of 40 minutes. The orange color soon gave way to a dark green color and a yellow solid precipitated. After the mixture had been refluxed for three hours, it was cooled and filtered. The bright yellow solid weighed 26.3 g. and melted over the range $280-300^{\circ}$. A recrystallization from 400 ml. of nitrobenzene yielded 25.2 g.

of the solid melting from 280 to 315°. By now it was apparent that the product was a mixture of at least two compounds. A separation was effected by refluxing the solid with two 400 ml. portions of glacial acetic acid and filtering hot. The cooled filtrates deposited a pale yellow solid melting at 323-325°. From pyridine (Norit) a colorless solid was obtained, m.p. 328.5-329.0°. Admixed with authentic 2-bromophenanthridone obtained by the bromination of phenanthridone, it melted undepressed.

The bright yellow solid remaining after the acetic acid extraction weighed 6.8 g. and melted at 298-300°. Several recrystallizations from nitrobenzene gave yellow needles, m.p. 301.0-302.5°. This may have been the substance isolated by Walls.

Anal. Found: N, 4.99, 5.00; Br, 28.75, 28.62.

The infrared spectrum showed no distinct NH band in the 2.9-3.2 μ region, but there were sharp bands at 5.9 μ (C=O), 6.3 μ (C=C), 9.3 and 9.45 μ , 11.9 and 12.2 μ , and 12.8 μ .

8. Sulfonation

a. Trial 1. In a 100 ml., round-bottomed flask equipped with a two-necked adapter were placed 20.0 g. (0.112 mole) of phenanthridine. An air condenser surmounted by a drying tube

was connected to one neck and an addition funnel placed in the other neck. In the course of 20 minutes 30 ml. of fuming sulfuric acid (15-18% SO_3) were added dropwise to the phenanthridine. The resulting mixture formed a warm, dark solution which was subsequently heated in an oil bath at $90 \pm 5^\circ$ for 30 hours. Upon cooling the mixture was poured cautiously into 100 ml. of water. After six hours in the cold 13.9 g. of white solid had precipitated. Additional cooling of this filtrate gave 1.5 g. of product. Dilution of the resulting filtrate with three volumes of water yielded 9.6 g. of sulfonic acid.

The total yield of product was 25.0 g. (81% calculated as phenanthridine sulfonic acid monohydrate). It was readily soluble in basic solution, and upon acidification was reprecipitated. Although a mixture of isomeric phenanthridine sulfonic acids seemed to have resulted, an homogeneous, cream-colored sample of a supposedly pure sulfonic acid was obtained by repeated solution in base and reprecipitation by acid. This latter product turned yellow when dried in an oven, but regained its cream color upon cooling in air. It was shown to be a monohydrate.

Anal. Calcd. for $\text{C}_{13}\text{H}_9\text{NO}_3\text{S} \cdot \text{H}_2\text{O}$: C, 56.27; H, 3.99; H_2O , 6.46. Found: C, 56.62, 56.60; H, 3.87, 4.03; H_2O , 6.42, 6.77.

b. Trial 2. The same apparatus and quantities were employed as in the preceding section; the heating period, however, was limited to 20 hours at 50°. Cooling the acidic aqueous solution gave no precipitate; consequently, the solution was made basic with sodium hydroxide to precipitate 16.2 g. (81% recovery) of phenanthridine, m.p. 100-103°.

D. Chemistry of Phenanthridone

1. Acetylation (attempted)

As other experiments had shown that phenanthridone was prone to electrophilic substitution at the 2- and 4- positions, the Friedel-Crafts acetylation of this system was attempted.

In a one-liter, three-necked flask equipped with a stirrer and a condenser connected with a gas trap were placed 19.5 g. (0.10 mole) of phenanthridone, 14.2 g. (0.18 mole) of acetyl chloride and 350 ml. of tetrachloroethane. Anhydrous aluminum chloride (41 g., 0.31 mole) was introduced in the course of 20 minutes. Hydrogen chloride was evolved as the reaction mixture became pale yellow in color. The suspension was stirred for six hours at incipient reflux, during which time more hydrogen chloride was given off and the contents changed to a dark, gummy solution. After this period the solution

was poured into a mixture of ice and concentrated hydrochloric acid. When the ice had melted, the tan suspension was filtered. After washing with ether and drying, the collected solid weighed 19.4 g. (99.5% recovery) and melted at 290-292°. A mixed melting point with authentic phenanthridone confirmed that it was starting material.

2. Bromination

Although the successful bromination of phenanthridone has been reported recently by Mosby (186), parallel studies were carried out by the author who was not immediately aware of the above communication. The following directions are essentially those of Mosby.

In a two-liter, three-necked flask equipped and trapped as in the chlorination of phenanthridone were placed 39.0 g. (0.200 mole) of phenanthridone and 400 ml. of glacial acetic acid. The suspension was stirred under reflux to attain solution. Then a solution of 35.2 g. (0.22 mole) of bromine in 100 ml. of glacial acetic acid was introduced dropwise over a two-hour period. Halfway through the addition period hydrogen bromide began to be evolved copiously. The resulting orange slurry was refluxed for five hours, whereupon the bromine color disappeared. The cooled mixture was poured

into two liters of water and the precipitated solid was collected. Thorough drying gave 53.8 g. (98%) of white powder melting over the range 315-319°. From 420 ml. of nitrobenzene white microneedles weighing 49.6 g. (91%) were obtained, m.p. 323-325°. The melting point for a fairly pure sample was 325.5-326.5°. However, repeated recrystallization from pyridine sometimes gave samples melting at 328.5-329.0°. The infrared spectrum showed prominent bands at the following positions (μ): 3.18 (NH), 5.95 (C=O), 11.1, 11.3, 11.5, 12.3, 12.9 and 13.9.

3. Chlorination

A one-liter, three-necked flask was equipped with a stirrer, condenser, and an addition funnel. The condenser led through a calcium chloride tube to a funnel inverted over sodium hydroxide solution. The flask was charged with 19.5 g. (0.100 mole) of phenanthridone, 0.5 g. of iron powder and 400 ml. of glacial acetic acid. Chlorine gas (10 g.) was dissolved in 200 ml. of glacial acetic acid and the resulting yellow solution was added to the stirred reaction mixture over one hour. The contents warmed somewhat and the initial orange color turned pale yellow. The suspension was stirred at room temperature for 20 hours, after which time it was

poured into two liters of water. The pale pink solid upon collection and drying weighed 23.5 g. and melted over the range 288-305°. In order to search for any lower melting 4-chloro isomer the solid was treated in a Soxhlet extractor with 300 ml. of absolute ethanol for nine hours. The residue in the thimble was a light pink solid weighing 18.2 g. (80%) and melting over the range 316-321°. Recrystallized from 470 ml. of pyridine (Norit) 14.5 g. (63%) of white 2-chlorophenanthridone, m.p. 326-327°, were obtained.

From the Soxhlet extracts 4.5 g. of pink solid were recovered, melting over the range 245-285°. By refluxing with 400 ml. of ethanol and filtering, an additional 2.0 g. residue of 2-chlorophenanthridone was obtained, m.p. 319-321°. The filtrate deposited 0.15 g. of tan powder, melting over the range 195-205°. This may be impure 4-chlorophenanthridone, but it could not be further purified. Thus, 20.2 g. (88%) of fairly pure 2-chlorophenanthridone were isolated. An analytical sample was obtained by recrystallization from pyridine, m.p. 327-328°.

Anal. Calcd. for $C_{13}H_8ClNO$: Cl, 15.45; N, 6.10.

Found: Cl, 15.57, 15.59; N, 6.05, 6.14.

The infrared spectrum of this chlorophenanthridone was almost identical with that of 2-bromophenanthridone. This

indicated that chlorination of phenanthridone occurred at the 2-position also.

4. Iodination

In a one-liter, three-necked flask equipped with a condenser, stirrer and solids funnel were placed 19.5 g. (0.100 mole) of phenanthridone, 11.1 g. (0.067 mole) of potassium iodide, 300 ml. of glacial acetic acid and 15 ml. of water. The temperature of the mixture was maintained between 55° and 60°, while 16.1 g. (0.075 mole) of potassium iodate were added portionwise over one hour. The iodine-colored suspension was then refluxed for seven hours, after which time most of the iodine color had faded. The solution was refluxed overnight and then poured into 1.5 l. of water. A little sodium sulfite was added to remove some residual iodine. Collection and drying of the solid gave 31.0 g. (96.5%) of fluffy, cream-white needles, m.p. 321-323°. Recrystallized from 225 ml. of nitrobenzene the shiny white needles weighed 28.4 g. (88.1%) and melted at 323-325°. An analytical sample was obtained from pyridine, m.p. 323.5-325.0°.

Anal. Calcd. for $C_{13}H_8INO$: I, 39.52; N, 4.36. Found: I, 39.40, 39.58; N, 4.33, 4.35.

As in the case of 2-chlorophenanthridone, the infrared spectrum of this iodophenanthridone was almost superimposable with that of 2-bromophenanthridone. This indicated that the iodine occupied the 2-position.

5. Mercuration (attempted)

Phenanthridone (19.5 g., 0.100 mole) mercury (II) acetate (30.9 g., 0.097 mole) and 400 ml. of glacial acetic acid were heated at the reflux temperature with stirring for 24 hours. Upon cooling, the pale yellow solution deposited 18.2 g. (93.3% recovery) of phenanthridone, m.p. 284-286°. Admixed with authentic phenanthridone, this product melted undepressed.

6. Nitration

The following procedure is an adaptation of the original directions of Moore and Huntress (219) and is advantageous for larger scale runs.

A 500 ml., three-necked flask fitted with a stirrer, condenser, and addition funnel was charged with 19.5 g. (0.100 mole) of phenanthridone. Over 25 minutes 244 ml. of concentrated nitric acid were added dropwise. A golden yellow

solution formed which gradually became orange-red in color. A definite evolution of heat was noticed 30 minutes after the addition. The reaction mixture rapidly turned to an almost unstirrable yellow suspension after which it was allowed to stand overnight. The paste was mixed with 500 ml. of water, and the solid was collected, washed well with water and dried. There resulted 23.1 g. (96%) of pale yellow solid, melting over the range 360-373°. The ground solid was extracted in a Soxhlet apparatus with 300 ml. of absolute ethanol. The residue was 19.8 g. (83%) of light cream-colored 2-nitrophenanthridone, m.p. 378-380°. From acetic acid a white powder was obtained, m.p. 382-383° with blackening.

The ethanolic extract upon cooling gave 3.0 g. of yellow 4-nitrophenanthridone, melting over the range 248-254°. Concentrating the solvent gave an additional 0.3 g. Recrystallizations from acetic acid gave bright yellow needles, m.p. 264-265°.

Evidence that the nitration products of phenanthridone are the 2- and 4-isomers was recently presented by two independent research groups (22, 185). Before this worker was acquainted with these results, he had undertaken an investigation of the then unknown nitrophenanthridones. Since the bright yellow nitro isomer melted some 30 degrees below phenanthridone (293°) itself, intramolecular hydrogen bonding

between the NH and NO₂ groups in this nitro isomer seemed likely. Its infrared spectrum supported such hydrogen bonding, as the NH band (3.2 μ) and the antisymmetric and symmetric nitro bands (6.6 and 7.5 μ) were shifted to longer wavelengths. Since intramolecular hydrogen bonding could only take place with 4-nitro isomer, 4-nitrophenanthridone was synthesized unequivocally as already indicated in Section C. By a comparison of infrared spectra and a mixed melting point determination the bright yellow nitrophenanthridone obtained in low yield from the nitration of phenanthridone was shown to be identical with this authentic 4-nitrophenanthridone.

7. Sulfonation

In a 200 ml., round-bottomed flask equipped with an air condenser were placed 19.5 g. (0.100 mole) of phenanthridone and 50 ml. of concentrated sulfuric acid. The dark-colored solution was heated in an oil bath at 150° for 18 hours. The cooled solution was poured onto 400 g. of ice and the resulting dark solution was refrigerated. When nothing came down, the solution was treated portionwise with 30 g. of powdered sodium bicarbonate. The solution was then heated to boiling and saturated with 15 g. of sodium chloride, whereupon a

cream-colored solid began to precipitate. The cooled suspension was filtered to give 34.6 g. of white solid. This was digested in a boiling solution of 500 ml. of water containing 60 g. of sodium chloride. Filtration gave 29.1 g. (98% based on the sodium salt) of white sodium phenanthridone sulfonate.

A *p*-toluidine salt was prepared by heating one gram of the sodium sulfonate, 0.5 g. of *p*-toluidine and two milliliters of concentrated hydrochloric acid in sufficient water to attain solution (200 ml.). The *p*-toluidine salt separated from the cooled solution as shiny, colorless needles, m.p. 283-284° with darkening.

The barium salt of this sulfonic acid was prepared and analyzed.

Anal. Calcd. for $C_{26}H_{16}BaN_2O_8S_2$: Ba, 20.02. Found: Ba, 20.07.

The infrared spectrum of the sodium salt exhibited bands at 3.2 μ (NH), 5.95 μ (C=O), 2.8, 8.5 and 9.5 μ (ionic sulfonate). The region from 12 to 16 μ resembled that of 2-bromophenanthridone; this indicates the sulfonic acid group was probably also attached to the 2-position.

8. Reaction with *n*-butyllithium

In a 500 ml., three-necked flask fitted in the usual manner were placed 9.8 g. (0.050 mole) of phenanthridone and 200 ml. of dry ether. Then 0.10 mole of *n*-butyllithium in 90 ml. of ether prepared in the usual manner was added over a period of 10 minutes. Spontaneous reflux and the formation of an opalescent orange solution characterized this period. The solution was stirred under reflux for 12 hours and then hydrolyzed. The ether layer was separated and the suspended solid extracted with 100 ml. of ether. The ether extracts upon drying had a pale blue fluorescence. The residual solid weighed 5.3 g. (54%) and melted over the range 270-276°. Recrystallization from 50 ml. of glacial acetic acid gave 4.4 g. of recovered phenanthridone, m.p. 290-292° (mixed melting point).

Removal of the ether from the extracts left a viscous, orange liquid which was subsequently dissolved in 30 ml. ethanol and treated with 50 ml. of saturated ethanolic picric acid solution. An initial darkening preceded the precipitation of 3.1 g. (13%) of yellow solid, m.p. 191-194°, dec. Recrystallization from a dioxane-ethanol pair gave stout, yellow needles, m.p. 195.5-197.5°, dec. Admixed with authentic 6-*n*-butylphenanthridine picrate (Section III, C, 1, a) this product melted undepressed.

9. Reaction with phosphorus pentachloride

Previous unsuccessful attempts of this worker to prepare 6-chlorophenanthridine had failed because of the rapidity with which the compound was solvolyzed when recrystallized from ethanol. Since such solvolysis, however, is acid-catalyzed (86), the product could be successfully purified from ethanol if some ammonium hydroxide were added to it.

In the same setup as used in the preparation of 6-n-propylphenanthridine, 9.8 g. (0.050 mole) of phenanthridone, 10.6 g. (0.050 mole) of phosphorus pentachloride and 20 ml. of phosphorus oxychloride were refluxed for five hours. Hydrogen chloride gas was evolved slowly. The phosphorus oxychloride was then distilled off under reduced pressure. The cream-colored residue was cautiously hydrolyzed with a mixture of 3 ml. of concentrated ammonium hydroxide and 50 ml. of water. The solid was filtered off and then extracted in portions with 300 ml. of ethanol containing 50 ml. of water and 4 ml. of concentrated ammonium hydroxide. The cooled extracts deposited 9.8 g. (92%) of white needles, m.p. 117.0-117.5°. Graebe and Wander (220) report a melting point of 116.5°.

E. Chemistry of Phenanthridone Derivatives

1. 2-Acetaminophenanthridone

In a one-liter, three-necked flask equipped with a stirrer and condenser were placed 20.0 g. (0.083 mole) of 2-nitrophenanthridone, 40.0 g. (0.61 g. atom) of zinc dust and 400 ml. of glacial acetic acid. The slurry upon stirring warmed considerably from the heat of reaction. After four hours the reaction mixture was heated at incipient reflux for six hours. The cooled mixture was poured into 600 ml. of water and the solid then filtered off. The product was extracted with glacial acetic acid in a Soxhlet apparatus. Filtration of the cooled acetic acid gave 17.2 g. (82%) of cream-colored solid, m.p. 358.0-359.5°.

Anal. Calcd. for $C_{15}H_{12}N_2O_2$: N, 11.01. Found: 10.90, 10.96.

The infrared spectrum exhibited bands at 3.1 and 3.2 μ (NH) and sharp bands between 5.95 and 6.05 μ (C=O).

2. Bromination of 2-acetaminophenanthridone

Two grams of 2-acetaminophenanthridone in 25 ml. of glacial acetic acid were treated with 1.8 g. of bromine in

5 ml. of acetic acid, and the mixture was warmed on the steam bath for ten minutes. The flocculent tan suspension was poured into water, treated with sodium hydrogen sulfite and filtered. The cream-colored solid weighed 1.55 g. and melted over the range 235-255°. Recrystallizations from pyridine gave matted, white needles, m.p. 286.0-286.5°, dec.

Anal. Calcd. for $C_{15}H_{11}BrN_2O_2$: Br, 24.13; N, 8.46.

Found: Br, 24.25, 23.92; N, 8.50, 8.35.

The infrared spectrum displayed bands at 3.1 and 3.2 μ (NH), 6.0 and 6.1 μ (C=O), 6.55 μ and 6.7 μ . The compound seemed to have the bromine atom at the 3-, or more likely, the 1-position.

3. Nitration of 2-acetaminophenanthridone

Two grams (0.0079 mole) of 2-acetaminophenanthridone in 25 ml. of glacial acetic acid were treated with a solution of 2 ml. of fuming nitric acid in 5 ml. of glacial acetic acid over a 15-minute period. Toward the end of this time 5 ml. of glacial acetic acid were added to fluidize the stiff yellow paste. After standing the mixture was diluted with water and filtered. The yellow product weighed 2.2 g. and melted over the range 333-340°. Two recrystallizations

from glacial acetic acid gave 1.4 g. (59%) of matted, pale yellow needles, m.p. 353.5-354.5°, dec.

Anal. Calcd. for $C_{15}H_{11}N_3O_4$: N, 14.13. Found: N, 14.13, 14.12.

The infrared spectrum showed bands at 3.1 μ (NH), 5.98 μ (C=O), 6.5 μ (NO_2), 6.58 μ and 6.7 μ . Analogous to the preceding bromination product, this compound seemed to be 2-acetamino-1-nitrophenanthridone.

4. 2-Chloro-5-methylphenanthridone

Solid potassium hydroxide (10 g.) was dissolved in 100 ml. of 95% ethanol. Then 5.0 (0.022 mole) of 2-chlorophenanthridone were added and the mixture warmed to attain solution. The solution was cooled somewhat and 10 ml. of methyl iodide were added. After ten minutes the clear, pale yellow solution changed to a thick white suspension. The cooled mixture was filtered and the solid washed successively with 95% ethanol and with water. Drying gave 4.7 g. (89%) of fluffy white solid, m.p. 191-192°. Recrystallization from 95% ethanol gave long, white, matted needles, m.p. 192-193°. Heacock and Hey (221) have prepared this compound from the suitably substituted N-methylbenzanilide by a Pechorr

synthesis. Their yield was poor, but they also reported a melting point of 192° .

5. 5-Methyl-2-nitrophenanthridone

2-Nitrophenanthridone (5.0 g., 0.021 mole) was stirred vigorously with 100 ml. of ethanolic potassium hydroxide solution. The resulting orange solid was filtered off and washed with ether.

The orange salt was suspended in 100 ml. of absolute ethanol in a 250 ml. flask. Methyl iodide (10 ml.) was added and the suspension was refluxed for 12 hours. The orange suspension soon became cream-colored. The reaction mixture was filtered to give 4.6 g. (87%) of cream-colored solid melting over the range $241-247^{\circ}$. By two recrystallizations from 95% ethanol pale yellow, matted needles were obtained, m.p. $248.5-249.5^{\circ}$. Heacock and Hey reported (222) the preparation of this compound in poor yield by a Pschorr synthesis from a suitable N-methylbenzanilide. Their melting point was also 249° .

Anal. Calcd. for $C_{14}H_{10}N_2O_3$: N, 11.02. Found: N, 11.26.

6. 2-Bromo-4-nitrophenanthridone

In a 250 ml., three-necked flask fitted with a stirrer and addition funnel were placed 10.0 g. (0.037 mole) of 2-bromophenanthridone. When concentrated nitric acid (125 ml.) was added over 30 minutes, heat was evolved and the suspension became yellow. The suspension was stirred for two hours, and then an additional one hour with gentle heating. The paste was mixed with water and the yellow solid collected and washed with water. The crude product weighed 11.8 g. and melted over the range 245-270°. Two recrystallizations from glacial acetic acid gave 6.8 g. (59%) of yellow needles, m.p. 282-284°. The analytical sample was obtained from pyridine as brilliant yellow needles, m.p. 284-286°.

Anal. Calcd. for $C_{13}H_7BrN_2O$: Br, 25.04; N, 8.78.
Found: Br, 25.19, 25.32; N, 8.74, 8.80.

The infrared spectrum exhibited bands at 3.2 μ (NH), 6.05 μ (C=O), 6.6 and 7.5 μ (NO₂). The shift in the nitro bands to longer wavelengths pointed to hydrogen bonding of the NO₂ and NH groups. Since this compound melted lower (by 40°) than 2-bromophenanthridone, the hydrogen bonding seemed to be intramolecular. Hence, the nitro group occupied the 4-position.

7. 2-Chloro-4-nitrophenanthridone

One gram (0.0037 mole) of 2-chlorophenanthridone and 12.5 ml. of concentrated nitric acid were warmed with frequent stirring on a hot plate for ten minutes. The suspension which had turned bright yellow was then allowed to stand. The mixture was diluted with water and filtered. Upon drying 1.2 g. of bright yellow solid melting over the range 248-270° was obtained. Two recrystallizations from 15 ml. portions of pyridine gave 0.75 g. (63%) of bright yellow needles, m.p. 278-281°. The analytical sample melted at 280-281°.

Anal. Calcd. for $C_{13}H_7ClN_2O_3$: Cl, 12.91; N, 10.20.
Found: Cl, 12.81, 12.90; N, 10.12, 10.18.

The infrared spectrum was quite similar to that of 2-bromo-4-nitrophenanthridone. Bands were present at 3.2 μ (NH), 6.01 μ (C=O), 6.58 and 7.45 μ (NO₂). Again the shifts in the nitro bands showed that there was hydrogen bonding between the NO₂ and NH groups. As this compound melted lower (by 45°) than 2-chlorophenanthridone, the hydrogen bonding seemed to be intramolecular. Such evidence indicated that this compound was 2-chloro-4-nitrophenanthridone.

8. Nitration of 2-iodophenanthridone

When 2-iodophenanthridone was subjected to nitration in hopes of obtaining 2-iodo-4-nitrophenanthridone, displacement of the iodine by the nitro group occurred.

One gram of 2-iodophenanthridone was warmed with 12.5 ml. of concentrated nitric acid. The suspended solid soon turned tan in color, and the supernatant liquid became reddish-brown. Upon further heating iodine crystals sublimed into the neck of the flask (detected with moist starch paper) and nitrous fumes were evolved. The cream-colored paste was diluted with water and filtered. After drying 1.15 g. of pale yellow solid were obtained which melted over the range 270-305°. This product was extracted with 30 ml. of hot glacial acetic acid. The residue was 0.50 g. of almost colorless solid, melting from 386-400°. Several recrystallizations from pyridine raised the melting point to 426-428°, dec. This compound contained halogen and seemed to be impure iodo-2,4-dinitrophenanthridone.

9. Reaction of 2-bromophenanthridone with n-butyllithium

In a one-liter, three-necked flask equipped with a stirrer, low-temperature thermometer and addition funnel

were placed 27.4 g. (0.10 mole) of 2-bromophenanthridone and 300 ml. of dry ether. The white slurry was cooled to -35° and 0.25 mole of *n*-butyllithium in 230 ml. of ether was added over the course of ten minutes. The chartreuse suspension was stirred for another ten minutes and then the mixture was allowed to warm up to 0° over 45 minutes. The resulting dark yellow solution was poured into a Dry Ice-anhydrous ether mixture. After the carbonation mixture had warmed to room temperature, the ether was removed, and the solid residue extracted with 400 ml. of 5% potassium hydroxide solution. The residual solid was re-extracted with 200 ml. of warm 5% potassium hydroxide solution. The combined basic extracts were acidified to precipitate 30.9 g. of a white solid which melted over 400° . Refluxing this product with glacial acetic acid gave 19.6 g. (82%) of another acid which melted at $361-363^{\circ}$ with darkening. Recrystallization of a sample from glacial acetic acid gave white prisms of the same melting point. This acid did not contain bromine and its neutral equivalent agreed with that of phenanthridone-2-carboxylic acid. The neutral equivalent was run in a sample previously dissolved in base and reprecipitated by acid. The white solid was dried at 150° for three hours. Since the acid was difficultly soluble in water, the titration was conducted on a sample suspended in warm 50% ethanol.

Anal. Calcd. for $C_{14}H_9NO_3$: neut. equiv., 239.22.

Found: neut. equiv., 238.

The infrared spectrum exhibited bands at 3.2μ (NH) and 6.05μ (C=O).

F. Reaction of Allylmagnesium Bromide with
the Azomethine Linkage

1. General procedure for the interaction of nitrogen
heterocycles with allylmagnesium bromide

The heterocycles employed in this study were of the purest grade commercially available. The pyridine was refluxed and distilled over a mixture of sodium hydroxide and barium oxide before use. The solid quinoxaline was also distilled (b.p. $99-100^\circ$ at 12 mm.) since it darkened upon storage. The acridine (m.p. $107-108^\circ$), phenanthridine (m.p. $105-106^\circ$) and benzalaniline (m.p. $55-56^\circ$) were used without further purification.

The allylmagnesium bromide was prepared in yields ranging from 79 to 88% (according to the quality of the allyl bromide) by following a published procedure (223). The reagent was analyzed by titrating a hydrolyzed aliquot with standard acid (224).

In order that the yields would be as indicative as possible of the heterocycle's activity, an arbitrarily chosen general set of directions was rigidly adhered to. (The case of benzophenone anil will be discussed separately.) Thus in a 500 ml., three-necked flask fitted in the usual manner were placed 0.175 mole of the heterocycle and 100 ml. of dry ether. (A solution was obtained except with acridine and phenanthridine.) To the stirred mixture was added 0.230 mole of filtered allylmagnesium bromide in ether (approximately one molar). In the case of quinoxaline 0.460 mole of the Grignard reagent was employed. Gentle reflux and the formation of a yellow to red precipitate characterized the 40-minute addition period. Thereafter, a complete solution was obtained, except for the pyridine and acridine runs where a yellow suspension persisted. The mixture was refluxed under nitrogen for 18 hours and then hydrolyzed with 500 ml. of saturated ammonium chloride solution. In all cases except acridine the product was ether-soluble. Hence, after separating the ether layer and extracting the aqueous layer with ether, the combined ether extracts were dried over anhydrous sodium sulfate and the ether subsequently removed. The residue was distilled under reduced pressure.

Since the product from acridine was only slightly soluble in ether, the hydrolyzed mixture was filtered to obtain

the crude product. An additional amount was obtained by removing the solvent from the dried ether layer. The crude solid was recrystallized from petroleum ether (b.p. 60-70°).

The yields of the products together with physical constants are given in Table 9. The yields are computed for the product after one purification (either distillation or recrystallization) and the physical constants after this purification were within two to three degrees of those given in Table 9.

a. 4-Allylpyridine. By distillation of the crude product there were recovered on two runs 50% and 70% of the

Table 9. Reaction of allylmagnesium bromide with compounds containing the azomethine linkage

Reactant	Product	Yield %	B.p.	(M.p.)
Pyridine	4-Allyl-	9	186-188°	(730 mm.)
Phenanthridine	6-Allyl-5,6-dihydro-	78	174-177°	(3.6 mm.)
Benzalaniline	α -Allylbenzylaniline	80	146-148°	(2.9 mm.)
Acridine	9-Allyl-9,10-dihydro-	81	---	(115-116°)
Quinoxaline	2,3-Diallyl-1,2,3,4-tetrahydro-	86	142-143°	(1.8 mm.)
Benzophenone anil	α -Allylbenzhydryl- aniline	95	---	(78.5-80°)

pyridine, respectively. Moreover, after the 4-allylpyridine had distilled over, some higher boiling tars remained in the reaction flask. The yield of 4-allylpyridine was 7-9% for the crude product, n_D^{20} 1.5170. An infrared spectrum of this product indicated the presence of weak NH bands. Bands characteristic of the $\text{CH}_2\text{-C}\equiv\text{C}$ group appeared at 10.05 and 11.0 μ . Presumably the product still contained some 4-allyl-1,4-dihydropyridine. The compound was purified and analyzed, therefore, as the picrate. The oxidizing action of the excess picric acid served to remove any residual dihydro compound. (Demonstration that this compound was the 4-isomer will be presented shortly.) The picrate was obtained as bright yellow needles from 95% ethanol, m.p. 167.5-168.5°. A mixed melting point with authentic pyridine picrate (m.p. 165°) melted over the range 140-150°, showing their nonidentity.

Anal. Calcd. for $\text{C}_{14}\text{H}_{12}\text{N}_4\text{O}_7$: N, 16.09. Found: N, 16.20, 16.23.

b. 6-Allyl-5,6-dihydrophenanthridine. The main fraction of the distilled product solidified upon cooling into 28.3 g. (78%) of pale yellow solid. This solid was recrystallized from 100 ml. of 95% ethanol to give 20.5 g. of cream-colored solid, m.p. 64-65°. Concentration and cooling of the filtrate gave an additional 6.5 g. of product. The

compound seemed quite prone to air-oxidation. When a sample was exposed to the atmosphere for a short period, the surface became yellow and eventually chartreuse. Consequently, the analytical sample was obtained from petroleum ether (b.p. 60-70°) as an almost white solid and dried in a desiccator under a nitrogen atmosphere, m.p. 64.5-66.0°.

Anal. Calcd. for $C_{16}H_{15}N$: N, 6.33. Found: N, 6.39, 6.34.

Examination of the infrared spectrum disclosed the following significant bands: 3.15μ (NH); 6.22μ (C=C), 13.25μ and 13.8μ (o-disubstituted benzene); 10.05 and 10.95μ ($CH_2-C=C$).

Additional support for the compound containing a dihydro group stemmed from the reaction of the compound with picric acid. When a warm ethanolic solution of the compound was treated with ethanolic picric acid solution, a vivid red solid precipitated. Attempted recrystallization of this red solid from 95% ethanol gave instead a brown solid of a wide melting range. As Ziegler and Zeiser (225) have observed, the picrates of dihydro derivatives are generally red in color. Presumably, during the attempted recrystallization the red dihydro picrate was slowly oxidized by the picric acid complexed with it.

c. α -Allylbenzylaniline. The product distilled over as 31.0 g. (80%) of pale yellow liquid. After fractionation through a short column a pure sample was used to obtain the following physical constants: n_D^{20} 1.5920 and d_4^{20} 1.0224. MR_D calcd.: 73.12. MR_D found: 73.90. The pale yellow liquid was fairly insensitive to air. The analytical sample was redistilled shortly before the analysis and kept in a sealed ampoule.

Anal. Calcd. for $C_{16}H_{17}N$: N, 6.27. Found: 6.08, 6.05.

The infrared spectrum of the compound run in bromoform contained these bands: 2.98 μ (NH); 3.3 μ , 3.35 μ and 3.5 μ (CH_2); 6.15 μ (C=C); 10.05 and 10.95 μ (CH_2 -C=C).

d. 9-Allyl-9,10-dihydroacridine. After one recrystallization from petroleum ether (b.p. 60-70°) the product was obtained as pale yellow needles, m.p. 113-116°. (After filtration there remained on the filter paper a small amount of olive green solid which was not investigated.) This compound did not have the pungency or sternutatory properties associated with acridine. The compound discolored somewhat on standing but seemed much less sensitive to air than the corresponding phenanthridine derivative. The analytical sample was obtained from petroleum ether (b.p. 60-70°) as cream-colored needles, m.p. 115-116°.

Anal. Calcd. for $C_{16}H_{15}N$: N, 6.33. Found: N, 6.32, 6.38.

The infrared spectrum exhibited bands at 3.0μ (NH), 6.25μ and 6.35μ ($C\equiv C$) and 10.1μ and 10.9μ ($CH_2-C\equiv C$).

As with the corresponding phenanthridine derivative, this compound gave a dark red solid when treated with ethanolic picric acid solution. The picrate melted with decomposition over the range $185-195^\circ$. Again, attempted recrystallization from ethanol changed the product to a dark tan solid, indicating the presence of a dihydro picrate.

e. 2,3-Diallyl-1,2,3,4-tetrahydroquinoxaline. The product was obtained as a pale orange liquid. It was fractionally redistilled and a sharp cut taken for physical constants: n_D^{20} 1.5855 and d_4^{20} 1.0301. MR_D calcd.: 69.51. MR_D found: 69.80. The compound was quite air-sensitive and short storage periods changed the clear, pale orange liquid to a dark red liquid. Consequently, the analytical sample was redistilled shortly before analysis and kept in a sealed glass ampoule.

Anal. Calcd. for $C_{14}H_{18}N_2$: N, 13.08. Found: 13.32, 13.32.

The infrared spectrum showed the following indicative bands when run in a capillary cell: 2.98μ (NH); 3.3μ and 3.5μ (CH_2); 6.13μ ($C\equiv C$); 10.1μ and 11.0μ ($CH_2-C\equiv C$).

f. α -Allylbenzhydriylaniline. The observations that benzophenone anil will not react with methyl, *n*-propyl and phenyl Grignard reagents under ordinary conditions, and reacts with phenylmagnesium bromide anomalously under forcing conditions, make its behavior with allylmagnesium bromide quite significant.

In a 500 ml., three-necked flask fitted in the standard manner were placed 43.3 g. (0.169 mole) of benzophenone anil suspended in 100 ml. of dry ether. Then 0.215 mole of allylmagnesium bromide in 100 ml. of ether was added over 25 minutes. Initially heat was evolved and the benzophenone anil began to dissolve. Soon, however, a white solid precipitated and spontaneous reflux continued. The mixture was stirred under reflux for 18 hours and then hydrolyzed with 500 ml. of saturated ammonium chloride solution. The pale yellow ether layer was separated and dried over anhydrous sodium sulfate. Removal of the ether and chilling of the residual oil gave 48.1 g. (95%) of light tan solid, melting over the range 72-78°. Recrystallization from 200 ml. of 95% ethanol gave 44.0 g. (87%) of white solid, m.p. 78.5-80.0°. It was assumed that allylmagnesium bromide added either 1,2 or 1,4 to benzophenone anil. That 1,2 addition had occurred, leading to α -allylbenzhydriylaniline, was demonstrated by subsequent experiments.

2. Structural proofs of the products

a. 2-Allylpyridine. In order to eliminate the 2-isomer as the product resulting from the interaction of pyridine with allylmagnesium bromide, the unequivocal synthesis of the previously unknown 2-allylpyridine was undertaken. The first attempt (226) employing the preparation of 2-pyridylmagnesium bromide and subsequent interaction with allyl bromide was unsuccessful. The second method, which was the reaction of allylmagnesium bromide with 2-bromopyridine, led to the desired compound.

1) Method 1. In a one-liter, three-necked flask equipped as usual were placed 10.0 g. (0.32 g. atom) of magnesium turnings. Then 2.1 ml. of ethyl bromide in 40 ml. of dry ether were added. Once the reaction had started, 31.4 g. (0.20 mole) of 2-bromopyridine and 10 g. of ethyl bromide dissolved in 200 ml. of dry ether were dropped in over a period of one hour. The dark brown suspension was stirred under reflux until no magnesium turnings were visible (1.5 hours). Then 38.7 g. (0.32 mole) of allyl bromide in 50 ml. of dry ether were introduced in 30 minutes. The extremely vigorous reaction was moderated by external cooling. After the reaction had subsided, the mixture was hydrolyzed with ammonium chloride solution. The dried ether extracts

were distilled to remove the solvent. The residue was distilled under water-pump vacuum to give the following fractions: 25-55° (1.5 g.); 55-100° (1.0 g.); 121-129° (1.5 g.). The residue in the flask weighed 6.0 g. and seemed to be a mixture of dipyridyls. A picrate was prepared from a portion of the residue, melting over the range 125-140°.

The fraction boiling from 25° to 55° at 12 mm. was converted to a picrate melting over the range 100-107°. This seemed to be impure 2-allylpyridine picrate.

11) Method 2. In a one-liter, three-necked flask equipped as usual was placed 0.235 mole of allylmagnesium bromide in 230 ml. of ether. To this Grignard reagent were added 34.8 g. (0.220 mole) of 2-bromopyridine in 125 ml. of dry ether while the flask was cooled in the ice-salt bath. During the 45-minute addition period the reaction mixture turned a vivid dark red. After stirring overnight the darkened mixture was hydrolyzed with saturated ammonium chloride solution. The ether layer was separated and dried over anhydrous sodium sulfate. After removal of the solvent the residue was distilled under reduced pressure. The product came over as a water-white liquid weighing 10.7 g. (40%), b.p. 59-65° at 12 mm. The product was redistilled and collected at 63-65° at 12 mm. n_D^{20} 1.5190. Since the base was

somewhat hygroscopic, it was stored and distilled over a mixture of sodium hydroxide and barium oxide before analysis.

Anal. Calcd. for C_8H_9N : N, 11.75. Found: N, 11.42. The picrate was prepared and recrystallized from 95% ethanol as golden yellow needles, m.p. 118.5-120.0°.

Anal. Calcd. for $C_{14}H_{12}N_4O_7$: N, 16.09. Found: N, 16.14, 16.25.

b. Hydrogenation of 4-allylpyridine. The allylpyridine obtained from the interaction of pyridine and allylmagnesium bromide was reduced to the corresponding n-propyl compound to demonstrate its identity with the 4-isomer.

In a 125 ml. hydrogenation flask were placed 200 mg. of platinum (IV) oxide, 40 ml. of 95% ethanol and a magnetic stirring rod. The catalyst was prereduced and then 0.67 g. of the allylpyridine in 25 ml. of 95% ethanol were introduced. After 191 ml. of hydrogen had been absorbed at 32° and 740 mm., the contents were filtered and concentrated to 15 ml. When 15 ml. of ethanolic picric acid solution were added, 0.60 g. of the picrate was obtained, m.p. 125.5-127.0° with sintering. When recrystallized from 95% ethanol long, yellow needles resulted, m.p. 128.0-129.5°. An authentic sample of 4-n-propylpyridine picrate was procured from Professor J. P. Wibaut (227) and was found to melt at 128.0-129.5°. When admixed with the above picrate, it melted

undepressed. Moreover, the infrared spectra of the two picrates were found to be identical.

c. Dichromate oxidation of 6-allyl-5,6-dihydrophenanthridine. One gram of 6-allyl-5,6-dihydrophenanthridine in 25 ml. of glacial acetic acid was heated to incipient reflux and treated with 3.9 g. of potassium dichromate over a period of 35 minutes. The contents were refluxed for an additional hour and then poured into 300 ml. of water. The tan solid upon collection and drying weighed 1.1 g. and melted over the range 265-275°. Recrystallization from glacial acetic acid (Norit) gave white needles, m.p. 291-293°. A mixed melting point with an authentic sample showed it to be phenanthridone. The formation of phenanthridone demonstrates the allyl group occupied the 6-position in the original compound.

d. Dichromate oxidation of 9-allyl-9,10-dihydroacridine. 9-Allyl-9,10-dihydroacridine (2.7 g.) was suspended in 25 ml. of hot glacial acetic acid. Over 20 minutes 5.3 g. of sodium dichromate were added. The green solution was refluxed for 45 minutes and then poured into 400 ml. of water. Filtration and drying gave 2.5 g. of dark tan solid, melting over the range 325-360°. The solid was sublimed from an evaporating dish to give bright yellow needles, m.p. 352-358° (some odor of acridine). Dissolved in hot 95% ethanol the solid yielded a markedly fluorescent blue solution. Cooling deposited bright

yellow platelets, m.p. 356-358°. Graebe (228) reports a melting point of 354° for acridone. The infrared spectrum showed the characteristic bands for NH (3.15 μ) and C=O (6.1 μ). This again offers evidence that in the original compound the allyl group was at the 9-position.

e. Reaction of *n*-propyllithium with benzophenone anil (α -(*n*-propyl) benzhydrylaniline). In a 250 ml., three-necked flask equipped as usual were placed 20.0 g. (0.078 mole) of benzophenone anil and 50 ml. of dry ether. Then 0.097 mole of *n*-propyllithium in 90 ml. of ether (prepared in 83% yield by following published directions for *n*-butyllithium) was added over a period of 45 minutes. The initial yellow suspension turned to a dark red solution and spontaneous reflux began. The solution was refluxed for six hours and then stirred overnight without heating. The reaction mixture was hydrolyzed with water and the pale green ether layer was separated and dried. Removal of the ether left 21.2 g. (91%) of pale green solid, melting over the range 69-74°. Recrystallization from 95% ethanol gave 18.0 g. (77%) of white solid, m.p. 83.0-84.5°. The analytical sample was obtained from 95% ethanol, m.p. 85.0-85.5°.

Anal. Calcd. for C₂₂H₂₃N: N, 4.64. Found: N, 4.70, 4.76.

f. Reduction of the hydrolyzed allyl Grignard adduct of benzophenone anil (conversion of α -allylbenzhydriylaniline to α -(n-propyl) benzhydriylaniline). The hydrolyzed allyl Grignard adduct of benzophenone anil was correlated with the hydrolyzed n-propyllithium adduct by reducing the former to the latter.

In the hydrogenating flask were placed 30 mg. of platinum (IV) oxide (Adams catalyst), 50 ml. of 95% ethanol and a magnetic stirring bar. After the catalyst was reduced, 3.0 g. (0.010 mole) of the hydrolyzed product of allylmagnesium bromide and benzophenone anil, and 50 ml. of ethyl acetate were added. After flushing the system, the compound was hydrogenated until one molar equivalent of hydrogen was taken up (40 minutes). The filtered solution upon concentration and refrigeration gave 2.5 g. (83%) of a cream-white solid, m.p. 83-85^o. A mixed melting point with the hydrolyzed n-propyllithium adduct of benzophenone anil showed these products to be identical. This shows that allylmagnesium bromide and n-propyllithium add to benzophenone anil in the same fashion. It remained to be confirmed that this was 1,2 addition.

g. Butyrophenone. This compound was conveniently prepared by adaptation from procedures for the preparation of other aliphatic-aromatic ketones (229).

In a one-liter, three-necked flask equipped as usual was placed 0.60 mole of filtered n-propylmagnesium bromide in 300 ml. of ether. To this was added a solution of 50.0 g. (0.485 mole) of redistilled benzonitrile in 60 ml. of dry ether over 45 minutes. The dark yellow solution was refluxed overnight and then poured into a mixture of 200 ml. of 6 N sulfuric acid and ice. The biphasic mixture was heated to distill off the ether and to hydrolyze the ketimine. The cooled mixture was extracted with ether and the extracts subsequently dried. The ether was removed and the residual oil distilled under reduced pressure. The butyrophenone came over at 106.5-107.0° at 13 mm. as a colorless liquid, 64.0 g. (90%).

h. Butyrophenone anil. This procedure is adapted from Reddellien's directions for acetophenone anil (230). The necessary aniline-zinc chloride complex was prepared by adding 25 ml. of freshly distilled aniline to a solution of 25.0 g. of zinc chloride dihydrate in 40 ml. of water, 20 ml. of ethanol and 10 ml. of concentrated hydrochloric acid. The white suspension was stirred thoroughly and then filtered. The solid was washed twice with ether and upon drying the white complex weighed 30.0 g.

Freshly distilled aniline (30 ml.) and butyrophenone (30.0 g., 0.202 mole) were mixed in a 200 ml., round-bottomed

flask and the flask was heated to 100° in an oil bath. Two grams of the aniline-zinc chloride complex were added and the bath temperature was slowly raised to 160° where it was maintained for 15 minutes. Steam began to evolve and continued to do so when the temperature was raised to 180° and held there for 30 minutes. The cooled mixture was taken up in 200 ml. of chloroform and filtered from the solid aniline-zinc chloride complex. The chloroform was distilled off and the residue was distilled under reduced pressure. After a forerun of aniline and butyrophenone, the butyrophenone anil came over as a clear yellow liquid weighing 15.8 g. (35%), b.p. $183-185^{\circ}$ at 13 mm., n_D^{25} 1.5926.

1. α -(n-Propyl) benzhydrylaniline. Phenyllithium was prepared in 99% yield according to published directions by the interaction of 2.2 g. (0.33 g. atom) of lithium wire and 22.8 g. (0.145 mole) of bromobenzene in dry ether.

In a 500 ml., three-necked flask fitted as usual were placed 0.144 mole of phenyllithium in 100 ml. of ether. To this were added 15.5 g. (0.069 mole) of butyrophenone anil in 75 ml. of dry ether over 50 minutes. The mixture was stirred for four hours and then refluxed for one hour. The reaction mixture was hydrolyzed and the ether layer was separated. The latter extracts were dried and the solvent was distilled off. The residue was 22.0 g. of a somewhat sticky, pale yellow solid. This solid was recrystallized from 95% ethanol to

give 12.4 g. (59%) of cream-colored product, m.p. 80-83°. Additional recrystallizations from 95% ethanol gave a white solid, m.p. 83-84°. Admixed with the n-propyllithium adduct of benzophenone anil, the product melted undepressed. Moreover, the infrared spectrum of this compound in carbon disulfide was also identical with that of the n-propyllithium adduct of benzophenone anil. This confirms that both allylmagnesium bromide and n-propyllithium add 1,2 to benzophenone anil.

G. Chemistry of Quinoline and Isoquinoline Derivatives

The synthetic utility of low-temperature, halogen-metal interconversion reactions with bromo-pyridines and -quinolines has been studied by previous workers in this Laboratory (231, 232). In this work the reaction was employed to prepare triphenyl-3-quinolytin by the formation of 3-quinolyllithium and subsequent reaction with triphenyltin chloride. The halogen-metal interconversion reaction was then extended to 4-bromoisoquinoline and led to the preparation of 4-benzoylisoquinoline.

1. Triphenyl-3-quinolytin

In a 500 ml., three-necked flask equipped with a stirrer, condenser and low-temperature thermometer was placed 0.13 mole of n-butyllithium in 89 ml. of ether. When the system had been cooled to -40° , 22.9 g. (0.11 mole) of 3-bromoquinoline in 100 ml. of dry ether (cooled solution) were added in three minutes. The dark red reaction mixture was stirred for 15 minutes at -45° to -35° , and then treated with 42.5 g. (0.11 mole) of triphenyltin chloride in 300 ml. of sodium-dried benzene in the course of five minutes. The temperature of the contents was allowed to rise to room temperature over a 2.5 hour period. During this time the color became orange and a yellow solid settled out of solution. The suspension was subsequently hydrolyzed and the separated organic layer was dried. The yellow oil remaining after removal of the solvent solidified partially upon refrigeration. The paste was filtered off and expressed from as much oil as possible. Recrystallization of the resulting solid from petroleum ether (b.p. $60-70^{\circ}$) gave 14.4 g. (27%) of yellow prisms melting from 111° to 115° . Another recrystallization from the same solvent yielded 12.5 g. (24%) of yellow crystals, m.p. $113-115^{\circ}$. Additional recrystallizations did not alter the melting point.

This product gave a positive test for an organotin compound (233) and left a white residue on strong ignition.

Anal. Calcd. for $C_{27}H_{21}NSn$: C, 67.82; H, 4.42; N, 2.92; Sn, 24.82. Found: C, 67.85, 68.04; H, 4.50, 4.51; N, 3.08, 3.03; Sn, 24.86, 24.86.

The picrate was prepared and formed glistening yellow plates when recrystallized from an ethanol-dioxane pair, m.p. $175.0-175.5^{\circ}$.

Anal. Calcd. for $C_{33}H_{24}N_4OSn$: N, 7.92. Found: N, 7.96.

The methiodide was prepared by warming the compound with methyl iodide in benzene solution. Recrystallization of the precipitated solid from ethanol gave a bright yellow solid, m.p. $183-184^{\circ}$, dec.

Anal. Calcd. for $C_{28}H_{24}INSn$: C, 54.23; H, 3.90. Found: C, 54.07; H, 3.98.

The hydrochloride was prepared by bubbling hydrogen chloride gas into a dry ether solution of the solid. Recrystallized from absolute ethanol, the white solid melted at $177.0-178.5^{\circ}$, dec. The molten sample resolidified and sublimed in excess of 225° .

2. Isoquinoline-4-carboxylic acid

In a 500 ml., three-necked flask equipped as described above was placed 0.090 mole of *n*-butyllithium in 65 ml. of ether. After cooling the contents to -35° , a precooled solution of 16.7 g. (0.080 mole) of 4-bromoisquinoline in 110 ml. of dry ether was added to the *n*-butyllithium in 15 minutes. The reaction solution turned dark red in the succeeding ten minutes at -35° . Then the mixture was poured quickly into a slurry of Dry Ice in anhydrous ether. The carbonation mixture was subsequently treated with 200 ml. of 1% potassium hydroxide solution. The aqueous layer was separated, boiled with Norit, filtered and acidified. The precipitated solid was collected and recrystallized from water. The dried acid weighed 6.1 g. (44%) and melted at $265-266^{\circ}$, dec. The reported value is $263-265^{\circ}$, dec.

3. 4-Benzoylisoquinoline

Analogous to the previous procedure, 0.090 mole of *n*-butyllithium in 73 ml. of ether was treated at -35° with 16.0 g. (0.077 mole) of 4-bromoisquinoline in 70 ml. of dry ether. After the dark red solution was stirred at -35° for 20 minutes, 8.0 g. (0.077 mole) of benzonitrile in 70 ml.

of dry ether were introduced. During a 40-minute period at -20° the reaction became orange and dark tars coated the flask. The mixture was then hydrolyzed and the separated organic layer was dried over anhydrous sodium sulfate. The red oil remaining after distillation of the solvent was heated for 30 minutes with 100 ml. of dilute hydrochloric acid. The cooled mixture was extracted with three 30 ml. portions of ether. The aqueous layer was made basic with sodium hydroxide and then extracted with chloroform. After drying the chloroform extracts the solvent was removed and the residue distilled under reduced pressure. The main fraction consisted of 6.7 g. (39%) of viscous red oil, b.p. $187-192^{\circ}$ at 4.5 mm. Upon cooling it solidified and melted over the range $70-75^{\circ}$. Recrystallization from dilute ethanol (Norit) yielded glistening white needles, m.p. $79-80^{\circ}$.

Anal. Calcd. for $C_{16}H_{11}NO$: N, 6.06. Found: N, 6.17.

The 2,4-dinitrophenylhydrazone derivative was prepared and recrystallized from an ethanol-ethyl acetate pair as reddish orange prisms, m.p. $207-208^{\circ}$.

Anal. Calcd. for $C_{22}H_{15}N_5O_4$: C, 63.92; H, 3.66; N, 16.94. Found: C, 63.85, 63.99; H, 3.64, 3.70; N, 16.81, 16.94.

The picrate was prepared and recrystallized from ethanol as yellow needles, m.p. $189.5-191.0^{\circ}$.

Anal. Calcd. for $C_{22}H_{14}N_4O_8$: C, 57.15; H, 3.05; N, 12.12. Found: C, 57.13, 57.23; H, 3.06, 3.09; N, 12.17, 11.99.

IV. DISCUSSION

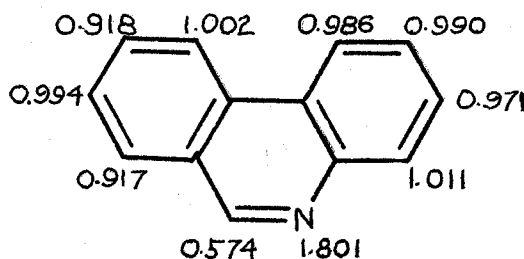
A. General Considerations

In the Historical Section of this dissertation the known chemistry of phenanthridine was considered in relation to that of other aza-aromatic heterocycles. In addition, a rationalization of the chemical behavior of these systems was developed in terms of modern views of molecular structure and chemical reactivity.

The present investigation was aimed at elucidating the fundamental chemistry of phenanthridine and certain of its derivatives. The aspects of this broad subject which have received special attention in this study include: (1) the electrophilic substitution of phenanthridine and phenanthridone; (2) the nucleophilic attack on the azomethine linkage of phenanthridine; (3) the dichromate oxidation of 6-alkylphenanthridines; (4) the synthetic possibilities of the foregoing processes; and (5) the comparison of the behavior of phenanthridine and other similar systems toward allylmagnesium bromide.

To facilitate the interpretation of experimental results, the following statements drawn from the discussion in Section II may be made. First, the overall reactivity of aza-aromatic

heterocycles toward electrophilic and nucleophilic attack increases in the order: pyridine < quinoline \simeq isoquinoline < phenanthridine \simeq acridine. Second, the site of nucleophilic substitution will be the carbon atom of lowest charge density (C_6 in phenanthridine). Third, the electrophilic reagents will tend to attack the heterocycles at positions of high charge density. The π electron density calculations of Longuet-Higgins and Coulson (54) for phenanthridine are given in (LXXI).



LXXI

Fourth, when there are several positions of high charge density such as C_4 , C_{10} , C_2 and C_8 in phenanthridine, the site of electrophilic substitution seems to be determined by the polarizability and the localization energy of that position. Generally speaking, a carbon atom of high polarizability, such as one in an "alpha" position (adjacent to another benzene ring), is more reactive.

Fifth, the experimental factors such as solvent, acidity, temperature and catalyst can exert a profound influence upon the course of reaction with aza-aromatic heterocycles. This effect may stem from changing the character of the substrate heterocycle (i.e., protonation of the nitrogen), or from altering the reactivity of the reagent.

Sixth, as one passes up the series from pyridones to phenanthridone, the keto tautomer becomes much more stable than the hydroxyl form. Consequently, one should expect phenanthridone to resemble benzanilide rather closely in its chemical behavior.

Seventh, alpha-substituted derivatives should increase in reactivity in the series, pyridine < quinoline \simeq isoquinoline < phenanthridine. Thus, 6-halophenanthridines undergo acid-catalyzed solvolysis extremely readily, and 6-alkylphenanthridines are easily oxidized with sodium dichromate in acetic acid.

Eighth, the localization energy of a given "double bond" becomes increasingly less as one goes to polycyclic aza-aromatic compounds. The superior stability of 5,6-dihydrophenanthridines compared with that of dihydropyridines is understandable, as the former compounds are formed with a proportionately smaller loss of conjugation energy.

B. Chemistry of the Phenanthridine System

1. Nucleophilic reagents

a. Alkylation and arylation. The reaction of organolithium compounds with phenanthridine offers an attractive route to the synthesis of 6-substituted phenanthridines. Gilman and Nelson (217) were able to obtain both 6-phenylphenanthridine and 6-p-tolylphenanthridine in excellent yields by use of this method. The dihydro intermediates formed subsequent to hydrolysis were oxidized with hot nitrobenzene after the manner of Ziegler and Zeiser (225).

In the present study it was clearly demonstrated that phenanthridine exhibits a high order of reactivity not only toward organolithium reagents, but to Grignard reagents as well. Indeed, both the reactive benzyl and allyl Grignard reagents gave 78% yields of the corresponding 6-substituted-5,6-dihydrophenanthridines, and even the less reactive n-propylmagnesium bromide gave 84% of 6-n-propylphenanthridine (subsequent to oxidation) when the reaction time was extended. The facility with which Grignard reagents react with phenanthridine is to be contrasted with the "forcing" conditions necessary to obtain the reaction of Grignard reagents with pyridine and quinoline. The latter heterocycles usually

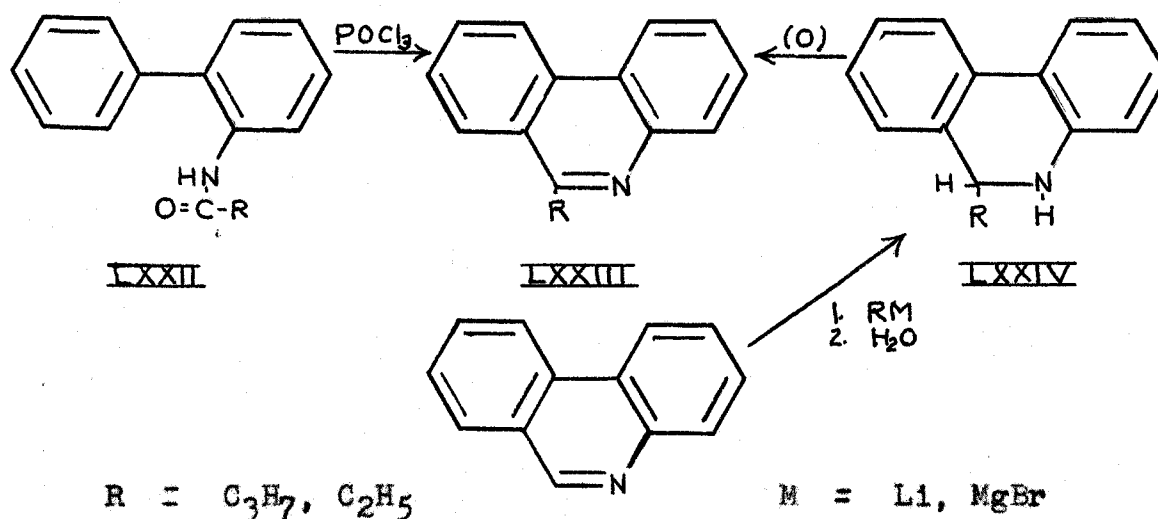
require stringent conditions such as the use of an autoclave (116), benzene-toluene systems (234) or dioxane mixtures (115). The selective action of allylmagnesium bromide on aza-aromatic heterocycles (Section IV, F) further emphasized the superior reactivity of phenanthridine compared to that of pyridine, quinoline, or isoquinoline.

As with other aza-aromatic heterocycles (225), *n*-butyllithium reacted with the azomethine linkage of phenanthridine with extreme rapidity. In an attempted metalation of phenanthridine at -50° with a 35-minute contact time, *n*-butyllithium gave instead a 90% yield of 6-*n*-butylphenanthridine (subsequent to nitrobenzene oxidation). A similar run at room temperature coupled with an 11-hour reflux period gave an 88% yield of the same product.

The mechanism of the reaction of organolithium compounds with the azomethine linkage probably involves the nucleophilic attack of the alkyl or aryl anion on the positive carbon atom. (Section II, C, 4). Although Grignard reagents seem to react by an analogous mechanism, it is established (120) that the organomagnesium reagent initially coordinates with the nitrogen atom to form a yellow, ether-insoluble complex. However, due to the lower charge and smaller radius of the lithium atom, coordination of the organolithium reagent with the nitrogen atom seems less favorable. Experimentally, no

precipitate is observed when RLi is added to ethereal solutions of nitrogen heterocycles.

Confirmation of the fact that both *n*-butyllithium and *n*-propylmagnesium bromide reacted with phenanthridine to give 6-alkylphenanthridines was established by the preparation and cyclization of the appropriate 2-acylaminobiphenyls. The synthetic samples of 6-*n*-butyl- and 6-*n*-propylphenanthridine (LXXIII) and their picrates proved to be identical with those obtained by the reaction of phenanthridine with the organometallic reagents.

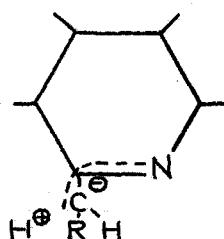


In the phenanthridine system certain dihydro intermediates such as (LXXIV) exhibited a high degree of stability. Such dihydro derivatives in the pyridine and quinoline systems are quite prone to air-oxidation, and are often

dehydrogenated in the course of working the reaction mixture up. The facility with which the dihydro product is oxidized seems to depend upon the amount of resonance energy recovered in forming the original aza-aromatic system. Indeed, there may be a gain in resonance energy if the new substituent is aromatic. For example, 6-phenyl-5,6-dihydrophenanthridine is smoothly oxidized by nitrobenzene to 6-phenylphenanthridine. Although the 6-phenyl substituent in the latter compound may not be exactly coplanar with the phenanthridine system, π -orbital overlap should still be appreciable.

On the other hand, certain phenanthridines such as 6-benzyl-5,6-dihydrophenanthridine and 6-alkyl-5,6-dihydrophenanthridines were not readily oxidized with nitrobenzene. It would seem that the exceptional stability of these and other dihydrophenanthridines may be due either to the insignificant gain in resonance energy obtainable by dehydrogenation, or to the steric hindrance to coplanarity of the 6-substituent. The former situation is illustrated by the fact that 6-n-butyl-5,6-dihydrophenanthridine was incompletely oxidized when heated with hot nitrobenzene. Infra-red analysis of the oxidized product showed the presence of a distinct NH band. 6-Benzyl-5,6-dihydrophenanthridine, moreover, was unchanged by refluxing with nitrobenzene. These observations are in accord with the results of Ziegler

and Zeiser (225) who found that nitrobenzene would not oxidize 9-alkyl-9,10-dihydroacridines. Similarly, Bergmann and Rosenthal (115) report that 9-benzyl-9,10-dihydroacridine resisted all attempts to oxidize it to 9-benzylacridine. In these examples the dehydrogenated product would gain only a small amount of stabilization by the hyperconjugation of the methylene group (LXXV). Thus, it seems that dehydrogenation is not too profitable energetically.



LXXV

The second factor contributing to the stability of certain dihydrophenanthridines, namely the steric impairment of coplanarity, may explain why 6-o-tolyl-5,6-dihydrophenanthridine can be isolated as a pure compound. In 6-o-tolylphenanthridine the spatial demands of the ortho methyl group would cause extensive interaction with the nitrogen and especially the hydrogen at C₇ if the o-tolyl group were coplanar with the phenanthridine system. Rotation of the o-tolyl to a position out of the plane diminishes this steric hindrance,

but also decreases the conjugation of the two systems. Since such steric interaction would be less in the dihydro derivative and as there is little resonance energy to be gained by dehydrogenation, the stability of 6-o-tolyl-5,6-dihydrophenanthridine is enhanced. The steric bulk of the ortho methyl group may account for the fact that when this compound is catalytically dehydrogenated and treated with picric acid, the resulting 6-o-tolylphenanthridine picrate melts abnormally low (m.p. 168°) in comparison with the picrate of 6-p-tolylphenanthridine (m.p. 228°).

b. Cyanation. Wittig and co-workers (127) have recently extended the Reissert procedure (126) to phenanthridine and have synthesized several 5-aroyl-6-cyano-5,6-dihydrophenanthridines. The reaction of phenanthridine methiodide with potassium cyanide, analogous to the Kaufmann cyanation of quinoline, was first carried out by Tinker (218) to procure 6-cyano-5-methyl-5,6-dihydrophenanthridine. As the latter worker was only interested in the spectral properties of this "pseudobase", he did not perform the subsequent oxidation leading to 6-cyanophenanthridine methiodide. This writer found that the dihydro compound of Tinker could be oxidized by iodine to give a 90% yield of 6-cyanophenanthridine methiodide. Interestingly enough, the infrared spectrum of this product did not exhibit the characteristic band of

the cyano group in the 4.5μ region. Confirmation of the fact that the cyano group does not always give a discernible band upon infrared analysis was obtained by examining the infrared spectrum of 4-cyanoquinoline methiodide. The latter compound also did not show a cyano group band in its spectrum.

The pyrolysis of 6-cyanophenanthridine methiodide under reduced pressure should lead to the formation of 6-cyanophenanthridine. This latter compound would have wide synthetic utility as it can be transformed into acid derivatives, ketones and alkylphenanthridines.

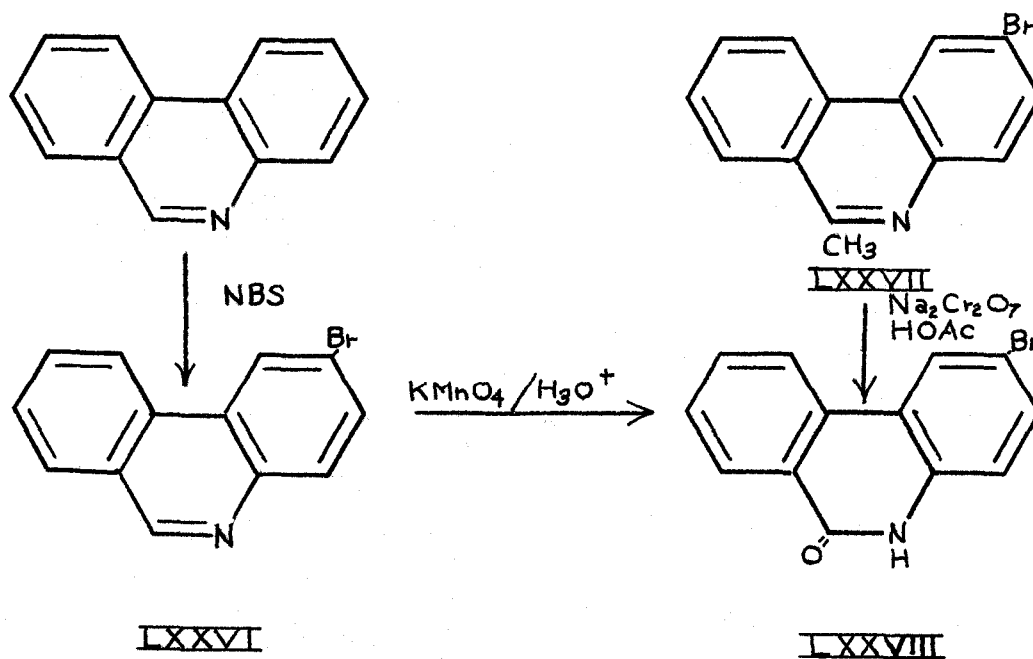
c. Hydroxylation. Analogous to the Chichibabin hydroxylation of pyridine, quinoline and isoquinoline it was found that phenanthridine readily underwent nucleophilic hydroxylation at the 6-position when heated with fused potassium hydroxide. This facile nucleophilic attack of the phenanthridine system may mean that future attempts to carry out the alkaline fusion of phenanthridinesulfonic acids will yield a mixture of the hydroxyphenanthridine and the hydroxyphenanthridone. Moreover, it would be interesting to study the behavior of certain groups such as nitro and halo in the alkaline fusions of substituted phenanthridines. If these groups are not displaced, this hydroxylation procedure may afford a superior method for converting phenanthridines to phenanthridones.

2. Electrophilic reagents

a. Bromination. In the study of the substitutional chemistry of phenanthridine in relation to other aza-aromatic heterocycles, it was considered of interest to attempt the bromination of this heterocycle. Contrasted with the nitration and sulfonation of quinoline which occur in the benzenoid ring, the bromination of quinoline generally takes place in the pyridinoid ring beta to the nitrogen. Since the pyridinoid ring in phenanthridine has no available position beta to the nitrogen, the position assumed by the entering bromine atom might help to elucidate the factors determining the exceptional selectivity of bromination.

As the direct bromination of phenanthridine has not been previously reported in the literature, the observation that phenanthridine and N-bromosuccinimide afforded a 31% yield of a monobromophenanthridine is significant. The same bromoisomer was also obtained by heating phenanthridine in acetic acid with bromine and by pyrolyzing phenanthridine hydrobromide perbromide. In addition, this bromophenanthridine was converted to a cyanophenanthridine by heating with copper (I) cyanide in quinoline. Examination of the infrared spectra of both the bromophenanthridine and cyanophenanthridine revealed the presence of a 1,2,4-trisubstituted benzene ring.

The proof of structure of this compound (LXXVI) was accomplished by oxidation with potassium permanganate in acid solution to give the corresponding bromophenanthridone (LXXVIII). The latter compound was shown to be identical with 2-bromophenanthridone by a mixed melting point determination and comparison of infrared spectra. The authentic 2-bromo-phenanthridone was prepared both by the bromination of phenanthridone and the dichromate oxidation of 2-bromo-6-methylphenanthridine (LXXVII). That phenanthridone yields the 2-isomer upon bromination was recently demonstrated by Mosby (186) and confirmed by independent studies of the writer. These reactions leading to the conclusion that the monobromophenanthridine is the 2-isomer are summarized in the following equations.



The bromination of phenanthridine still requires additional study in order to determine optimal preparative conditions and to search for isomeric bromophenanthridines. The pyrolysis of phenanthridine hydrobromide perbromide yielded some higher melting products which may be polybromo isomers. The heightened reactivity of the phenanthridine nucleus probably accounts for its being brominated under such mild conditions as N-bromosuccinimide in carbon tetrachloride. As the 2-position is one of higher charge density (although not the highest; see (LXXI)), it is probable that the actual bromination of phenanthridine is of an electrophilic nature. If the bromination were to proceed by a free-radical mechanism, one would expect 6-bromophenanthridine to be the major product, by analogy with pyridine and quinoline.

b. Nitration. The significance of solvent and temperature on the course of a substitution reaction is apparent in the nitration of phenanthridine. When Caldwell and Walls (22) dissolved phenanthridine nitrate in cold, concentrated sulfuric acid and separated the six mononitrophenanthridines formed, they obtained a 3% yield of 2-nitrophenanthridine. In the present investigation this worker was able to isolate a 9% yield of 2-nitrophenanthridine by heating phenanthridine nitrate in a mixture of acetic anhydride and acetic acid at 80°. This enhanced reactivity of the 2-position in the latter

solvent is explicable both in terms of the higher temperature favoring attack at less reactive positions and of the less acidic solvent decreasing the reactivity of the nitrating species.

c. Sulfonation. When it is recalled that acridine is sulfonated only with difficulty at 200° (112), the facility with which phenanthridine is sulfonated is somewhat surprising. The preliminary sulfonation experiments described in the Experimental Section demonstrate that phenanthridine undergoes sulfonation at a relatively low temperature with 15% fuming sulfuric acid and that at least two, and possibly more, isomeric phenanthridinesulfonic acids are formed. One isomeric sulfonic acid has been isolated in pure form as the monohydrate. This latter acid is soluble in hot, but not in cold, water. Although the orientation of this latter acid is not known, the writer feels it is probably the 4-isomer, by analogy with quinoline-8-sulfonic acid which is also the least soluble of the quinolinesulfonic acids (235).

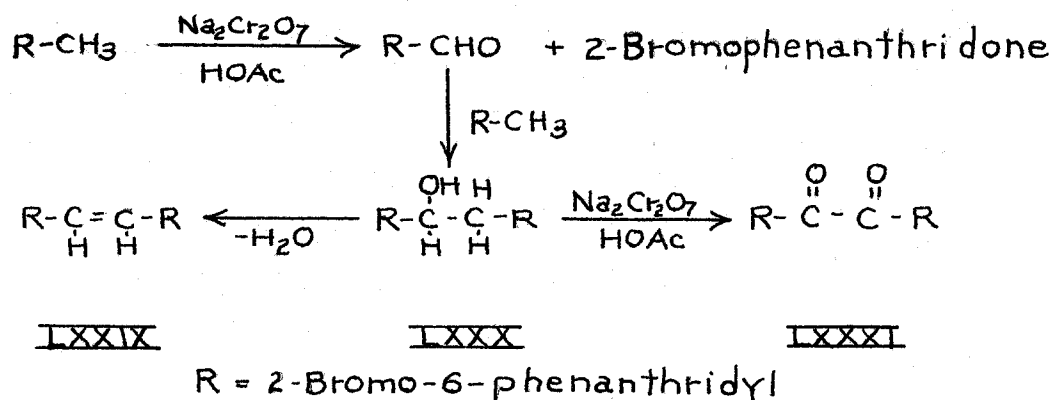
Further investigation of this sulfonation process should furnish valuable results, not only in opening up pathways to different derivatives but also in conferring water-solubilizing properties upon future dyes and pharmaceuticals.

3. Dichromate oxidation of 6-alkylphenanthridines

The dichromate oxidation of 6-methylphenanthridines was first employed by Walls (16) to prepare substituted phenanthridones. This behavior of 6-methylphenanthridines is to be contrasted with that of 2-methylquinolines where dichromate oxidation yields carboxylic acids. A mechanism may be proposed which involves the oxidation of the 6-methylphenanthridine to the 6-carboxylic acid and the subsequent decarboxylation of this alpha acid. The phenanthridine thus formed could then be oxidized to the phenanthridone. However, it was shown in this study that phenanthridine is essentially unchanged when subjected to prolonged heating with sodium dichromate in glacial acetic acid. Consequently, the phenanthridine is probably not an intermediate.

The phenanthridones prepared by this method are often contaminated with highly colored by-products. For example, Walls prepared both 2-bromophenanthridone and 2-nitrophenanthridone by the oxidation of the appropriate 6-methylphenanthridines. 2-Bromophenanthridone was described as being a bright yellow solid melting at 302°, and 2-nitrophenanthridone was reported to be a brick-red product melting over 350°. In connection with the bromination of phenanthridone the writer repeated Walls' procedure for the preparation of

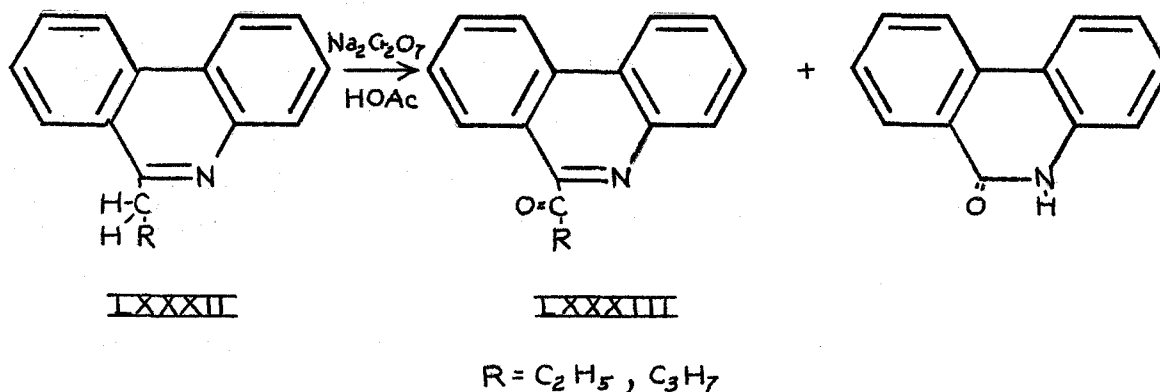
2-bromophenanthridone and found that the "yellow product" was actually a mixture of white 2-bromophenanthridone (m.p. 329°) and a bright yellow solid (m.p. 301°). It seems that the latter product was actually the one reported by Walls. This unknown compound may be formed in one of the following reactions.



The ethene by-product (LXXIX) has actually been isolated in the selenium dioxide oxidation of certain 6-methylphenanthridines (236), but since the infrared spectrum of the yellow substance had a pronounced band at 5.9 μ , the presence of a carbonyl group was indicated. As the bright yellow color was in accord with the alpha dicarbonyl structure of (LXXXI), the compound was reacted with o-phenylenediamine to give a quinoxaline derivative, confirming the presence of an alpha diketone linkage. These observations indicate that

the yellow product melting at 301° is probably di-(2-bromo-6-phenanthridyl) glyoxal (LXXXI).

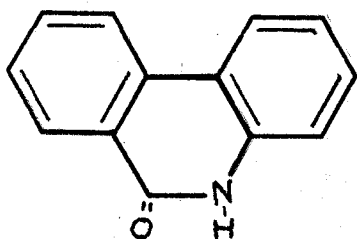
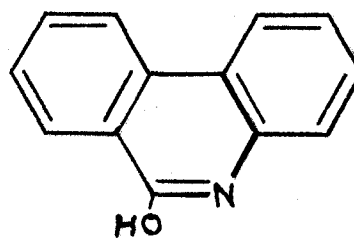
When the dichromate oxidation reaction was extended to other 6-alkylphenanthridines, both phenanthridone and the corresponding 6-acyl derivative were formed. In this manner 6-butyrylphenanthridine and 6-propionylphenanthridine (LXXXIII) were isolated from the corresponding 6-alkylphenanthridines (LXXXII).



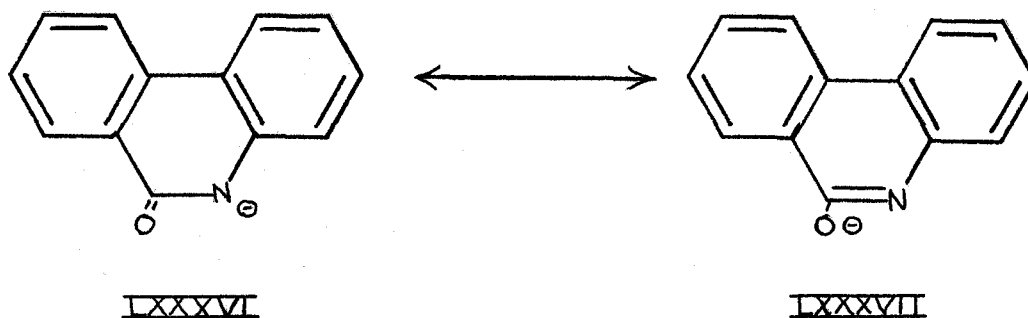
The dichromate oxidation of 6-alkylphenanthridines under milder conditions may well furnish an excellent route for the preparation of 6-acylphenanthridines. This method was employed to demonstrate that benzylmagnesium chloride added to the azomethine linkage of phenanthridine, for the dihydro adduct could be smoothly transformed to the known 6-benzoylphenanthridine in 72% yield.

C. Chemistry of the Phenanthridone System

The structure of phenanthridone is better represented as a cyclic amide of 2-aminobiphenyl-2'-carboxylic acid (LXXXIV), rather than as 6-hydroxyphenanthridine (LXXXV). The infrared spectrum shows bands characteristic of an NH and C=O of an amide group. There is no evidence to support any mobile equilibrium between these two possible tautomers.

LXXXIVLXXXV

As with other electronegatively substituted amides, the hydrogen of the NH group is sufficiently acidic to make phenanthridone soluble in alcoholic, but not aqueous, potassium hydroxide solution. This dissolution occurs without hydrolysis of the amide linkage, as aromatic resonance stabilizes the anion and diminishes the polarity of the carbonyl group (LXXXVI, LXXXVII).



In contrast to that of phenanthridine the substitutional chemistry of phenanthridone is relatively simple. The participation of the unshared electron pair on the nitrogen with the aromatic pi electrons is possible in the case of phenanthridone. Since the hydrogen of the NH group occupies an sp^2 orbital (as in pyrrole) the unshared nitrogen electrons are in a p orbital. Hence, resonance delocalization should enhance the charge density at C₄, C₂, C₁₀ and C₈. Such activation should cause phenanthridone to resemble benzanilide in its behavior.

At the outset the writer intended to employ the analogy with benzanilide to develop the chemistry of phenanthridone. The only substitution reaction then reported was the nitration of phenanthridone, originally carried out by Moore and Huntress (219). These workers isolated two nitrophenanthridones which were shown to be neither the 3- nor the 8-isomers. The present study began with the reasonable premise that these

unidentified products were the 2- and 4- isomers. The bright yellow nitrophenanthridone was suspected of being the 4-isomer because of its relatively low melting point and the hydrogen bonding indicated by its infrared spectrum. As both facts taken together suggested strong intramolecular hydrogen bonding, the nitro group seemed to be adjacent to the NH group. As this was only possible with the 4-isomer, the authentic 4-nitrophenanthridone was prepared from 6-methyl-4-nitrophenanthridine (215) and was shown to be identical with the yellow nitration product of phenanthridone.

This conclusion indicated that the cream-colored nitration product of phenanthridone should have been the 2-isomer. However, 2-nitrophenanthridone had been described as a red solid (16). (Walls and Caldwell (22) later showed the pure compound was really cream-colored.) Consequently, the 10-nitrophenanthridone was synthesized unambiguously in hopes that it was the higher-melting, cream-colored nitration product of phenanthridone. However, comparison of infrared spectra and melting points of these two nitrophenanthridones showed they were different.

In parallel studies phenanthridone upon bromination gave an excellent yield of a monobromophenanthridone. Again it was felt that this product was the 2-isomer. Although Walls reports that 2-bromophenanthridone was bright yellow,

repetition of the oxidation of 2-bromo-6-methylphenanthridine by the writer showed that Walls' product was a mixture of 2-bromophenanthridone and probably di-(2-bromo-6-phenanthridyl) glyoxal, as previously discussed. The white 2-bromophenanthridone isolated was shown to be identical with the bromination product of phenanthridone.

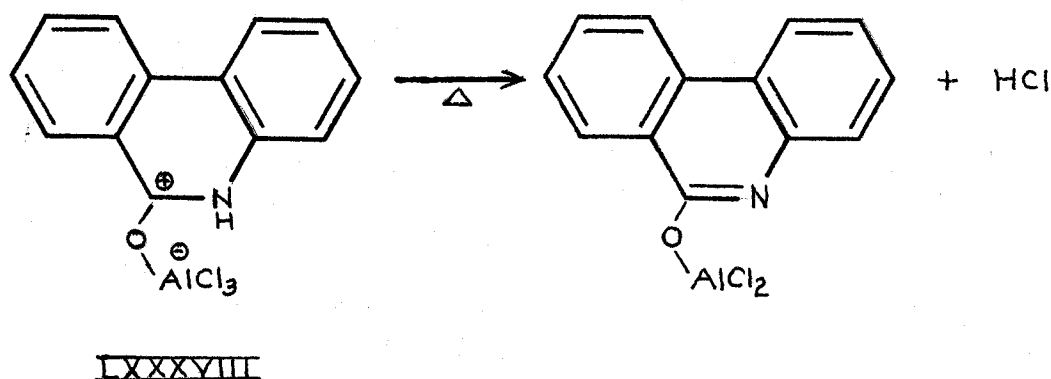
Publications on the nitration (22) and bromination (186) of phenanthridone have recently appeared which identified the nitrophenanthridines as the 2- and 4-isomers, and the bromophenanthridone as the 2-isomer. The writer thus has largely confirmed these reported conclusions, but has done so in a different manner.

The other electrophilic substitution reactions of phenanthridone considered in the present study were alkylation, chlorination, iodination, mercuration and sulfonation. Phenanthridone underwent chlorination extremely readily to give an 88% yield of 2-chlorophenanthridone. In a similar fashion 2-iodophenanthridone was obtained in 97% yield by heating phenanthridone in glacial acetic acid with an iodide-iodate mixture. That both chlorination and iodination also occurred at the 2-position was indicated by the similarity of their infrared spectra with that of 2-bromophenanthridone.

The sulfonation of phenanthridone was easily accomplished by heating it with concentrated sulfuric acid to obtain

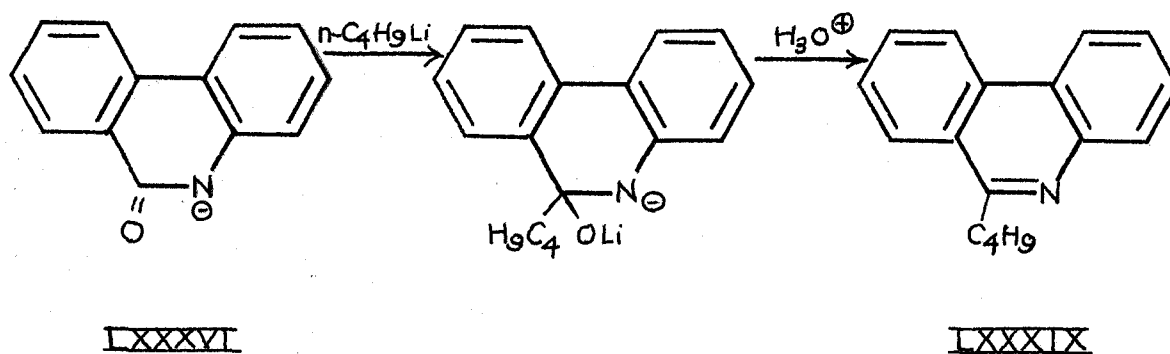
almost a quantitative yield of phenanthridone-2-sulfonic acid.

The ease with which phenanthridone underwent substitution in the foregoing reactions suggested that perhaps this system could be acetylated in a Friedel-Crafts reaction. Although hydrogen chloride was evolved when phenanthridone was heated in tetrachloroethane with acetyl chloride and aluminum chloride, the phenanthridone was recovered in a quantitative manner. It is likely that the amide group reacted with the aluminum chloride to form a complex (LXXXVIII) which deactivated the system.



The nucleophilic alkylation of the carbonyl group in phenanthridone is not easily realized. For example, when phenanthridone was refluxed in ether solution with two equivalents of *n*-butyllithium, only a 13% yield of 6-*n*-butylphenanthridine (LXXXIX) (isolated as the picrate) was obtained

and 54% of the phenanthridone was recovered unchanged. The stability of the anion initially formed (LXXXVI) probably accounts for the diminished reactivity of the carbonyl group.

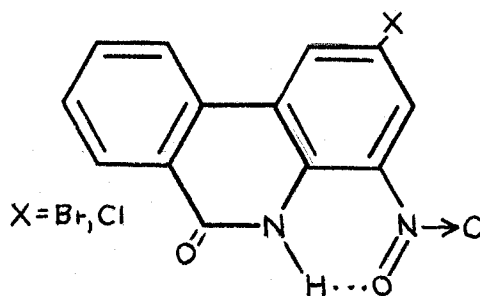


D. Chemistry of Phenanthridone Derivatives

1. Nitration of 2-substituted phenanthridones

In consequence of its nitro group being adjacent to the NH group, 4-nitrophenanthridone has a bright yellow color, a much lower melting point than phenanthridone, and an infrared spectrum exhibiting shifts due to hydrogen bonding. This collection of properties furnishes excellent criteria for the detection of a 4-nitro group in substituted phenanthridones. Thus when either 2-bromo- or 2-chloro-phenanthridone was nitrated, the product was a bright yellow solid melting some 40° below the initial halophenanthridone and its spectrum

showed marked shifts in the nitro bands indicative of hydrogen bonding. Consequently, the nitration must have occurred at the 4-position, yielding the 2-halo-4-nitrophenanthridone (XC).



XC

When, however, 2-iodophenanthridone was nitrated in an analogous fashion, displacement of the iodo group occurred as evidenced by the iodine liberated. Although the product of this reaction melting at 426° was never obtained pure, the infrared spectrum and elementary analysis indicated this solid may be an (8- or 10-) iodo-2,4-dinitrophenanthridone. Presumably 2-iodo-4-nitrophenanthridone was first formed and the iodine subsequently displaced to give 2,4-dinitrophenanthridone. In the presence of iodine and nitric acid this molecule might have been iodinated at the 8- or 10-position.

2. Alkylation of substituted phenanthridones

Graebe and Wander (220) report that phenanthridone may be N-alkylated by fusing the amide with potassium hydroxide

to obtain the potassium salt and heating the latter with the appropriate alkyl halide in a sealed tube. The writer found, however, that certain negatively substituted phenanthridones such as the 2-nitro and 2-chloro derivatives could be readily methylated by heating the amide with methyl iodide in ethanolic potassium hydroxide solution. The success of this procedure seems to depend on the phenanthridone being a stronger acid than ethanol and the amide anion being alkylated faster than the solvent.

3. Halogen-metal interconversion with 2-bromophenanthridone

As was pointed out in the reaction of n-butyllithium with phenanthridone, the diminished reactivity of the carbonyl group in basic medium is explicable in terms of the resonance-stabilization of the amide anion. Utilization of this fact was made in the halogen-metal interconversion reaction between 2-bromophenanthridone and n-butyllithium. Subsequent carbonation of the product gave an 82% yield of phenanthridone-2-carboxylic acid.

E. Synthesis of Phenanthridine Derivatives

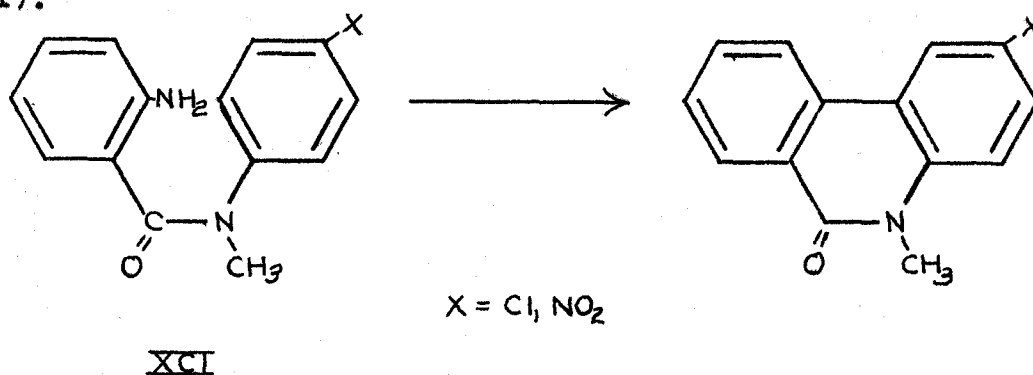
Present synthetic approaches to the phenanthridine system center largely around the Morgan-Walls cyclization of

2-acylaminobiphenyls. Although this method is quite versatile, the appropriate 2-aminobiphenyl is often difficult to synthesize and sometimes the subsequent ring closure does not take place smoothly. Direct substitution on phenanthridine and phenanthridone systems offers an attractive, alternate method to the synthesis of derivatives. Both phenanthridine and phenanthridone are now readily available: the former from either coal tar or the cyclization of 2-formaminobiphenyl (237); the latter by the cyclization of 2-biphenyl isocyanate (238).

Phenanthridine could possibly be nitrated under modified conditions to vary the proportions of the isomers. Although the separation might be tedious, the nitrophenanthridines would furnish access to the 1-, 2-, 3-, 4-, 8- and 10-derivatives. Moreover, bromination of phenanthridine with N-bromosuccinimide may well be quite selective; further study may demonstrate that 2-bromophenanthridine may be prepared in satisfactory yield.

The electrophilic substitution of phenanthridone serves as an excellent way to obtain the 2-bromo-, 2-chloro-, 2-iodo-, 2-nitro and 2-sulfonic acid isomers. In addition, certain 2-substituted derivatives as the 2-bromo- and 2-chlorophenanthridones can be nitrated in the 4-position.

The utility of such substitution reactions is evident by comparison with some recent work of Heacock and Hey (221, 222). In their studies of the Pschorr reaction these authors were able to prepare 5-methyl-2-nitrophenanthridone and 5-methyl-2-chlorophenanthridone in very low yield by the diazotization and coupling of the corresponding amino benzanilides (XCI).



In contrast with this, phenanthridone can be nitrated to give 83% of 2-nitrophenanthridone and this in turn upon methylation yields 87% of 5-methyl-2-nitrophenanthridone. Likewise, phenanthridone upon chlorination gives 88% of 2-chlorophenanthridone and this compound can be methylated in 89% yield to form 5-methyl-2-chlorophenanthridone.

The reductive acetylation of 2-nitrophenanthridone results in 2-acetaminophenanthridone in 82% yield. This latter compound has been successfully nitrated and brominated, but the resulting compounds have not been definitely identified.

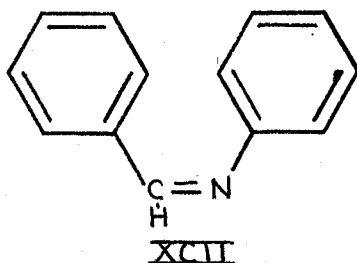
In consideration of the superior activating power of the acetamino group, it is felt that substitution occurred ortho to this group. Of the two possible positions (1- and 3-), the 1-position may well be favored due to the superior reactivity of such an "alpha" position. If this is so, 1-substituted derivatives would be accessible by deamination of the substituted 2-aminophenanthridones.

F. Reaction of Allylmagnesium Bromide
with the Azomethine Linkage

The addition of organometallic compounds to conjugated anils has been found to occur in two principal ways: either the reagent adds 1,2 to the azomethine linkage; or 1,4 to the conjugated system. This is exemplified by the behavior of benzophenone anil with phenyllithium and with phenylmagnesium bromide. The former reagent readily adds 1,2 to form tri-phenylmethylaniline upon hydrolysis; the latter reagent reacts with difficulty by 1,4 addition and forms upon hydrolysis o-phenylbenzhydrylaniline. Similar studies with α, β -unsaturated ketones have led to the conclusions that reactive organometallic compounds add 1,2 with facility, whereas less reactive organometallic compounds add principally 1,4 and with greater difficulty (239).

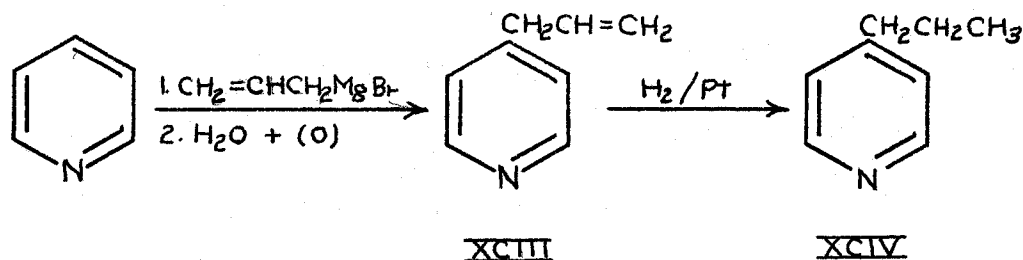
In this study the reaction of allylmagnesium bromide with various compounds containing the azomethine linkage was carried out. The results emphasize the fact that the occurrence of 1,4 addition depends not only upon the reactivity of the organometallic compound, but also upon the reactivity of the nitrogen substrate. For example, pyridine reacted with allylmagnesium bromide to give only a 9% yield of 4-allylpyridine, whereas benzophenone anil gave a 95% yield of the 1,2 adduct with the same reagent.

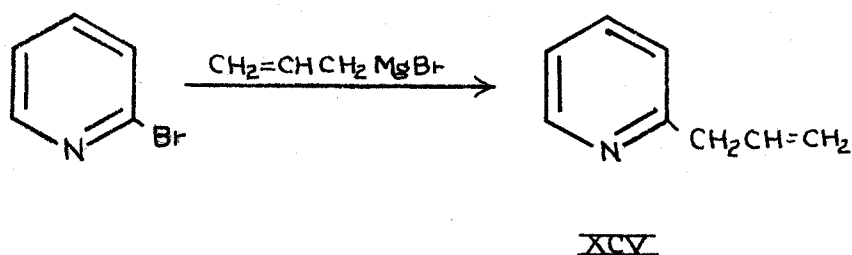
Under the same conditions, the reactivity of the nitrogen compounds toward allylmagnesium bromide increased in the order: pyridine < quinoline \simeq isoquinoline < phenanthridine \simeq acridine \simeq benzalaniline < quinoxaline < benzophenone anil (74). It is significant that the diaza-aromatic heterocycle, quinoxaline, showed a higher reactivity than any monoaza-aromatic type. The presence of two electronegative heteronitrogens enhances the polarity of the C=N linkage. In order to compare an open-chain model of an aza-aromatic system with these heterocycles, benzalaniline (XCII) was examined as the open model of phenanthridine.



The reactivity of the two compounds was about of the same order. Interestingly enough, benzophenone anil showed an extremely high order of reactivity.

The position assumed by the entering allyl group was always alpha or gamma to the nitrogen atom. It might be expected that pyridine would form the 2-isomer by analogy with the reaction of n-butyllithium on this heterocycle (225). However, that the 4-isomer (XCIII) resulted was demonstrated by hydrogenating the compound to the corresponding n-propylpyridine (XCIV) and comparing the melting point and infrared spectrum of the picrate with that of authentic 4-n-propylpyridine picrate (227). A mixed melting point of the two solids showed no depression. (It is realized that the mixed melting point determination is occasionally unreliable in showing the identity of picrates (240). The conclusions, however, are never based solely on this criterion). Moreover, 2-allylpyridine (XCV) was prepared unambiguously from 2-bromopyridine and allylmagnesium bromide and was shown to differ from the hydrolyzed product of pyridine and allylmagnesium bromide. The following equations summarize these transformations.

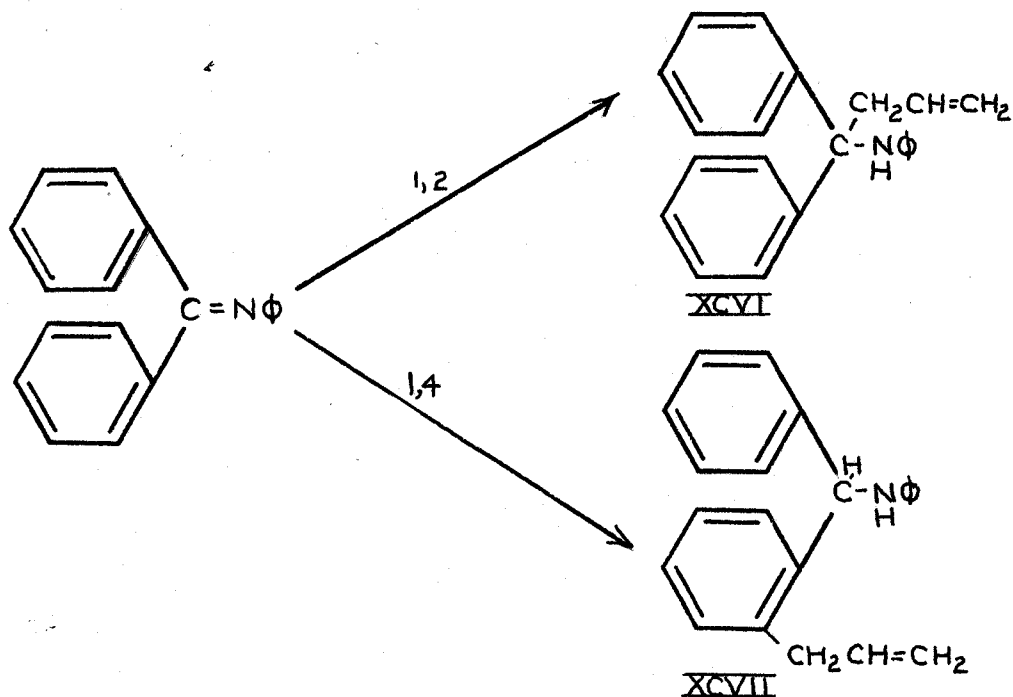




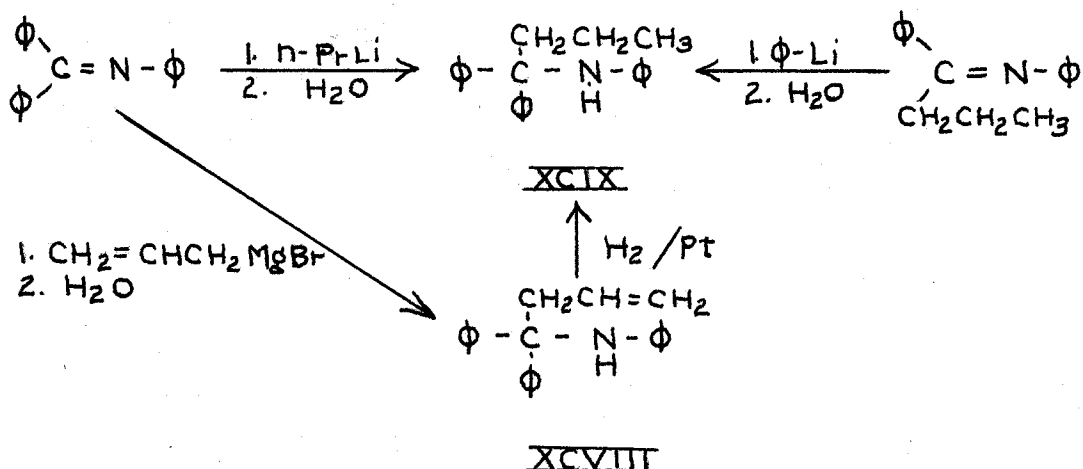
Additional support for these conclusions is derived from the report that benzylmagnesium chloride and pyridine also form the 4-isomer (117), instead of the 2-isomer as originally reported by Bergmann and Rosenthal (115).

In the cases of phenanthridine, acridine, benzalaniline and quinoxaline only one mode of attack was considered possible, that is, on the available carbon, alpha or gamma to the nitrogen. (Isoquinoline is presumably not attacked at C_3 but only at C_1 .) However, dichromate oxidation of the products from phenanthridine and acridine furnished independent proof that the allyl group occupied the available position in the pyridinoid ring. Dichromate oxidation studies of phenanthridine and its derivatives indicate that if there is an alkyl group at the 6-position in phenanthridine, oxidation will produce phenanthridone. Thus, since the supposed 6-allyl-5,6-dihydrophenanthridine upon such treatment gave phenanthridone, the allyl group must have been at the 6-position. In a similar fashion 9-allyl-9,10-dihydroacridine gave acridone.

The product from allylmagnesium bromide and benzophenone anil could conceivably be the 1,2 (XCVI) or the 1,4 adduct (XCVII).



Demonstration that both allylmagnesium bromide and n-propyllithium added to benzophenone anil in a 1,2 manner was accomplished by: (1) hydrogenating the allyl Grignard product (XCVIII) to the n-propyllithium product (XCIX) and (2) synthesizing α -(n-propyl) benzhydrylaniline unambiguously and showing it to be identical with the propyllithium adduct of benzophenone anil.



Since the methyl, *n*-propyl and phenyl Grignard reagents do not react with benzophenone anil under analogous conditions, the high reactivity of the allyl Grignard reagent is apparent.

The probable mechanism of the reaction of Grignard reagents with aza-aromatic heterocycles has already been discussed (Section II, D, 3, a). Moreover, an explanation has been given for the preferential attack of Grignard reagents on the gamma position in pyridine (Section II, C, 4). In order to rationalize the marked difference in reactivity of aza-aromatic heterocycles toward allylmagnesium bromide, it is profitable to consider the loss in resonance energy in the course of reaction. When the Grignard reagent reacts with the $-\text{C}=\text{N}-$ group, the linkage is removed from conjugation with the rest of the aromatic system. This results in a certain

loss in resonance energy. The greater the "double-bond" character of an azomethine linkage, the less should be this loss in resonance energy. Consequently, such a system should exhibit a greater reactivity toward allylmagnesium bromide. The large "double-bond" character of the azomethine linkage in benzophenone anil, phenanthridine and benzalaniline explains the ease with which they react with allylmagnesium bromide. In systems such as pyridine, quinoline and isoquinoline the azomethine linkage has less "double-bond" character due to the considerable resonance delocalization; consequently, the heterocycles show a low order of reactivity with this Grignard reagent.

V. SUMMARY

The modern theoretical views of molecular structure and reaction mechanisms have been freely invoked to rationalize the chemical and physical properties of pyridine, quinoline, isoquinoline, acridine and phenanthridine.

The substitution and addition reactions of aza-aromatic heterocycles have been discussed as to relative ease of reaction, probable mechanism and agreement of experimental findings with theoretical predictions. The importance of factors such as the nature of the reagent and experimental conditions has been evaluated. Quantum mechanical charge density calculations have shown only limited utility in predicting sites of substitution in these heterocycles. An alternate theoretical approach would consider variations in the energy and geometry of the reaction transition state.

The chemical and physical properties of alpha and gamma derivatives of aza-aromatic heterocycles have been compared. The possible tautomerism of amino, hydroxyl and methyl derivatives has been discussed in terms of the available experimental data.

The behavior of phenanthridine toward certain electrophilic and nucleophilic reagents has been examined, and the following conclusions have been reached.

1. The azomethine linkage exhibits a high order of reactivity toward organolithium and organomagnesium reagents.
2. Phenanthridine can be readily hydroxylated by the Chichibabin procedure to give phenanthridone.
3. Phenanthridine methiodide is transformed by the Kaufmann procedure to 6-cyanophenanthridine methiodide.
4. Treatment of phenanthridine with N-bromosuccinimide or other brominating agents affords a moderate yield of 2-bromophenanthridine.
5. Heating phenanthridine nitrate with acetic anhydride and acetic acid gives an improved yield of 2-nitrophenanthridine.
6. Phenanthridine is sulfonated under relatively mild conditions to form two or more isomeric sulfonic acids, one of which seems to be the 4-isomer.

In an analogous fashion the chemistry of phenanthridone was investigated and was found to have the following characteristics.

1. Phenanthridone is readily halogenated to give the 2-bromo, 2-chloro- and 2-iodophenanthridones in excellent yield.

2. The nitration of phenanthridone gives as the minor product a yellow solid which is shown to be 4-nitrophenanthridone.
3. The carbonyl group of the amide linkage has a low order of reactivity and prolonged treatment of phenanthridone with n-butyllithium gives a small yield of 6-n-butylphenanthridine.
4. Although phenanthridone can be sulfonated in a quantitative fashion, the system does not undergo Friedel-Crafts acetylation under the usual conditions.

Substituted phenanthridones were shown to possess synthetic utility. First, 2-halophenanthridones could be conveniently nitrated to yield 2-halo-4-nitrophenanthridones. The position of the nitro group was demonstrated by consideration of spectral data and physical properties. Second, certain negatively substituted phenanthridones, such as 2-chlorophenanthridone, could be N-methylated under very mild conditions. Third, the diminished reactivity of the carbonyl group in 2-bromophenanthridone allowed the preparation of phenanthridone-2-carboxylic acid by the halogen-metal interconversion reaction.

The dichromate oxidation of certain 6-alkylphenanthridines to obtain phenanthridones gave interesting by-products.

From the preparation of 2-bromophenanthridone by this method a bright yellow product was isolated which seems to be di-(2-bromo-6-phenanthridyl) glyoxal. When the reaction was conducted with 6-n-butylphenanthridine, both phenanthridone and 6-n-butyrylphenanthridine were isolated. Other compounds such as 6-n-propylphenanthridine and 6-benzyl-5,6-dihydro-phenanthridine also gave ketones.

The reactivity of a series of aza-aromatic heterocycles and anils toward allylmagnesium bromide increased in the following order: pyridine < phenanthridine \simeq benzalaniline \simeq acridine < quinoxaline < benzophenone anil. In all cases 1,2 addition to the azomethine linkage occurred, except for pyridine and acridine where 1,4 addition took place.

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